The native cardiac output in human sepsis: a systematic review

Luca Cioccari, Nora Luethi, Ulrike Weber, Andrew Hilton, Jukka Takala and Rinaldo Bellomo

ABSTRACT

Background: The cardiac output (CO) response to sepsis is typically measured in the intensive care unit after modification by fluid and/or vasoactive drug resuscitation and found to be hyperdynamic. In contrast, the native (pre-resuscitation) CO in human sepsis is poorly defined.

Design and data sources: Systematic literature review of studies reporting the cardiac index (CI) of patients with sepsis before resuscitation, using searches of PubMed, MEDLINE and Embase.

Results: We identified 5667 citations from 1929 to 2014. Of 179 articles meeting inclusion criteria, only four studies reported CO measurements before any treatment, in a total of 181 patients. Only two of the four studies reported age distribution (mean age, 72 years) for a total of 159 patients. We calculated the mean CI in these four studies to be 2.68 L/min/m^2 (SD, 0.42 L/min/m^2; median, 2.52 L/min/m^2; range, 2.36–3.3 L/min/m^2). Only one study presented mixed venous oxygen saturation data as an estimate of the adequacy of perfusion, and in three studies there was evidence of reduced cardiac performance.

Conclusion: Data about the native CO in human sepsis are scant because therapeutic intervention usually precedes measurement. From the limited data available, it appears that most patients are in a normodynamic haemodynamic state at presentation, and cardiac performance also seems to be impaired at the earliest stage of sepsis. As initial resuscitation is partly predicated on assumptions about the underlying cardiovascular physiology, our findings suggest the need to address this knowledge deficit in the management of patients with severe sepsis.

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The cardiovascular response to sepsis has been the subject of intensive investigation over the past 50 years. Before the advent of bedside haemodynamic monitoring, two distinct types of septic shock were described: an early phase of warm shock, characterised by increased pulse pressure and a warm periphery; and a late phase of cold shock, characterised by decreased pulse pressure and a cold periphery.[1,2] With the introduction of the pulmonary artery catheter, it became widely accepted that, after fluid resuscitation, most patients with septic shock have a hyperdynamic circulation (supranormal cardiac output [CO] and low systemic vascular resistance).[3] This was shown to occur despite a reduced biventricular ejection fraction and decreased volume responsiveness.[4-6]

There is a subgroup of patients who develop a hypodynamic response, with reduced CO and myocardial depression.[7,8] Because greater survival from septic shock appeared associated with a higher CO,[9-11] therapeutic strategies to achieve or maintain a hyperdynamic state have been commonly proposed over the past 40 years.[12] This is advocated despite a lack of evidence of benefit[13,14] and uncertainty on how best to assess the adequacy of cardiac index (CI).

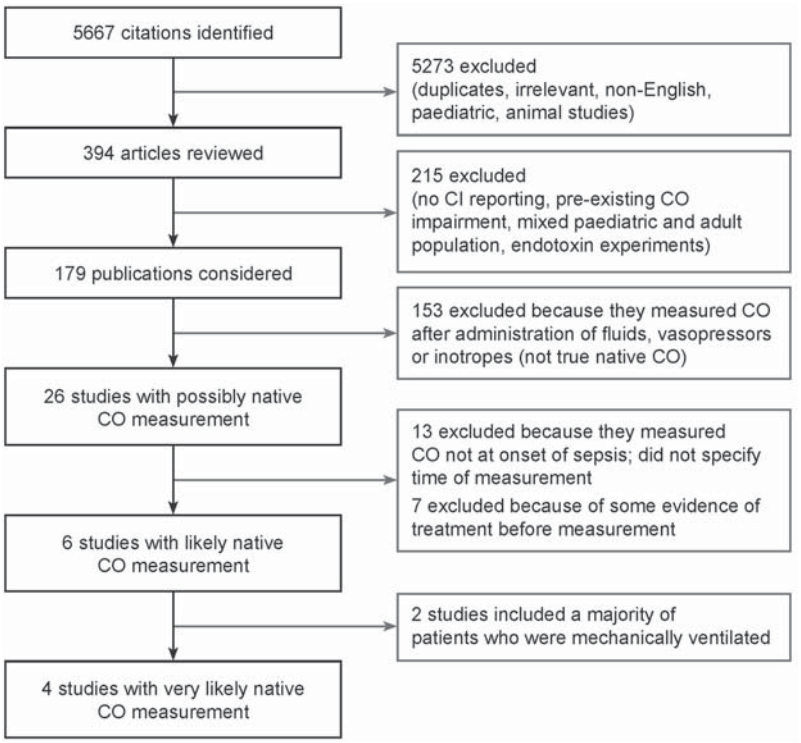
In response to septic hypotension, most clinicians first administer fluids. This approach would be physiologically logical if a patient's pre-treatment CO was low (hypodynamic state), ventricular preload low or normal and cardiac contractility adequate. In contrast, if contractility was the predominant problem, early initiation of inotropes and cautious fluid administration may be more appropriate. Similarly, if the patient's CO was already high at presentation, vasopressor therapy would be the most physiologically logical intervention. Thus, understanding what is known about the pre-treatment (native) CO in patients with sepsis would be a useful first step in informing clinicians on the most physiologically likely circulatory state and the possible contributors to hypotension.

Methods

We conducted a comprehensive English literature search using three electronic databases (PubMed, MEDLINE and Embase) in October 2014 with the search terms "cardiac output" or "cardiac index" and "sepsis" or "severe sepsis" or "septic shock". Selective hand searching, reference lists and our personal archives were used to identify additional studies of potential relevance. A summary of the review process is outlined in Figure 1.

Three of us (L C, N L and U W) assessed identified citations for relevance using the information provided in the title, abstract, descriptor and MeSH terms. We independently reviewed the abstracts of potentially relevant studies and the manuscripts of those meeting our inclusion criteria, and the study was included when agreement was reached.

Figure 1. Identification of studies reporting cardiac index in sepsis



CI = cardiac index. CO = cardiac output.

Study inclusion criteria

We focused on the native CO in sepsis. We defined native in this context as the CO measured as early in the course of sepsis as possible (ie, before intubation, fluid resuscitation or initiation of vasopressor or inotropic support). We screened all randomised controlled trials and cohort and case–control studies reporting numeric CIs of adult patients with sepsis, severe sepsis or septic shock. We excluded those that did not fulfil our definition of native CO, categorising the remainder as possibly, likely or very likely having native CO measurements.

We also systematically excluded paediatric and animal studies; studies that included mixed populations (eg, including patients with and without sepsis, or including adults and children) if the COs of the group with sepsis or the adult group were not reported separately; volunteer endotoxin infusion studies; and trials focusing only on sub-populations of patients with conditions known to independently affect CO, such as severe heart or liver failure and post-operative patients.

To allow comparison between different patient groups, we only included studies that reported indexed values of CO as the crude, mean or median CI. Studies reporting CI only in graphic format were included only if the exact value could be ascertained.

Reference to normal age-related values

We defined whether a cardiovascular state was hypodynamic, normodynamic or hyperdynamic using the age band of 60 to 65 years as the reference age, because of findings from the three recent pivotal randomised controlled trials of early goal-directed therapy.[15-17] We defined a CI < 2.2 L/min/m^2 as representing a hypodynamic state, a CI of 2.2–3.7 L/min/m^2 as representing a normodynamic state and a CI ≥ 3.7 L/min/m^2 as representing a hyperdynamic state. These definitions were in accordance with accurate cardiovascular magnetic resonance imaging data and derived reference values for normal humans at rest in this age group.[18,19]

Data collection

Two of us (L C and N L) independently extracted the data using a standardised form and resolved disagreements by discussion. For each study, we extracted data on patient population, study type, study location, study setting, study interventions, method used for CO measurement and individual study exclusion criteria. We identified patient age, data on administration of intravenous fluids, vasopressors and inotropes, and data on use of mechanical ventilation before CO measurements were taken. Where available, we also collected data on heart rate and mean arterial pressure (MAP) at the time of CO measurement.

Statistical analysis

The variety of study types and protocols and the heterogeneity of the results precluded a meta-analytical approach. Therefore, our results are reported as means and SDs or medians and interquartile ranges (IQRs), with full ranges where appropriate. SEM was converted to SD by using the formula SD = SEM × $\sqrt{n}$. For studies including patient groups of unequal size, mean and median values were adjusted for the number of patients per group.

Results

Search results

We identified 5667 citations published over an 86-year period from 1929[20] to October 2014. Of these, 5273 were excluded as duplicates, irrelevant, non-English or including children, non-septic patients or animals. Of the 394 potentially relevant manuscripts, 179 met our inclusion criteria. The study characteristics are summarised in Table 1.

Table 1. Summary of all studies reporting cardiac index in human sepsis

Study characteristic	Data
Total number of studies	179
Variable	
Median patients per study, n (IQR)	23 (15–37)
Mean patient age, years (SD)	58.5 (8.1)
Mean APACHE II score (SD)	23 (4)
Mean mortality, % (SD)	49% (21%)
Mean cardiac index, L/min/m^2 (SD)	3.9 (0.9)
Mean arterial pressure, mmHg (SD)	70 (14)
Mean heart rate, beats/min (SD)	102 (17)
Mean body temperature, °C (SD)	37.9 (0.4)
Setting	
Intensive care unit or shock unit	164
Ward	6
Laboratory or research unit	4
Emergency department	1
Type	
Observational	74
Retrospective	9
Interventional	102
Multicentre	13
Study of endotoxins	4
Method	
Pulmonary artery catheter	120
Indocyanine green	24
Calibrated pulse contour analysis	18
Echocardiography	15
Uncalibrated pulse contour analysis	3
Fick method	3
Other	2
Not reported	3
Use of mechanical ventilation	
Mechanically ventilated	114
Not ventilated	6
Not reported	59
Administration of fluids	
Fluids administered	129
Not reported	21
Use of vasoactive agents or inotropes	126
Noradrenaline	103
Dobutamine	61
Dopamine	61
Adrenaline	27
Not reported	11

IQR = interquartile range. APACHE = Acute Physiology and Chronic Health Evaluation.

Confounding interventions

Most of the 179 studies (114/179 [64%]) included ventilated patients. Data on mechanical ventilation were absent in 59 papers. Intravenous fluids, vasopressors or inotropes were administered in 153 studies (85%) before or at the time of the first haemodynamic assessment.

Data on fluid resuscitation were highly inconsistent. Most studies simply acknowledged that intravenous fluids had been given, reporting the use of crystalloids or colloids without further details on dose and time of administration. In studies stating the exact amount of fluid given, the dose varied between 250 mL[21] and more than 5000 mL.[3] These interventions led to us excluding those studies.

Relevant studies with possibly native CO measurements

Of the 179 included studies, 26 clinical studies did not use or report the use of fluids or vasoactive medications before CO measurement (Table 2).[7,22-46] These trials included a total of 748 patients (mean age, 59.5 years; SD, 9.3 years) and reported a median CI of 3.24 L/min/m^2 (range, 1.4–4.98 L/min/m^2). Data on CI and heart rate reported in these studies are shown in Figure 2 and further details are shown in the Appendix.

On detailed scrutiny, 19 of these 26 studies did not measure CO at onset of sepsis or had some evidence of treatment before CO measurement (Table 3). Overall, the time point of CO measurement was highly variable. Six studies did not specify the exact time of haemodynamic assessment.[7,27,28,30,34,41] In other studies, only average CO values over the whole study period were reported.[23,40,46] Seven studies included therapeutic interventions before the first assessment.[24,26,31,32,35,39,46] Four studies either excluded unstable patients or allowed a period of haemodynamic stabilisation before CO measurements.[22,26,33,39] All these studies were considered unlikely to represent native CO values and were excluded.

Probable and likely true native CO measurements

We identified six publications reporting the CO in patients with sepsis on presentation. Two of these six studies included a majority of mechanically ventilated patients.[29,37] The remaining four reported a mean CI of 2.68 L/min/m^2 (SD, 0.42 L/min/m^2; median, 2.52 L/min/m^2; range, 2.36–3.3 L/min/m^2) (Table 4).[36,38,44,45] Shoemaker and colleagues found a mean CI of 2.36 L/min/m^2 (SD, 0.9 L/min/m^2) in a subgroup of 10 patients with sepsis, and stroke volume was markedly reduced in this cohort (mean, 37.3 mL; SD, 13 mL).[38] In 1965, Wilson and colleagues studied 12 hypotensive patients with sepsis and found a median CI of 3.3 L/min/m^2 (IQR, 2.35–4.55 L/min/m^2).[45] One patient in this series was hypodynamic and five (42%) were hyperdynamic. We cannot exclude the possibility that some of these

Table 2. Setting, design and size of studies with possibly native cardiac output measurements

First author	Journal, year	Setting	Location	Study type	Patients, *n*	Patient condition
Berre[22]	*Critical Care Medicine*, 1997	ICU	Belgium	Prospective	14	Sepsis
Castagneto[23]	*Circulatory Shock*, 1983	ICU	Italy	Prospective	36	Sepsis
Clowes[24]	*American Journal of Surgery*, 1978	Surgical ward	US	Prospective	38	Severe sepsis
Dahn[25]	*Surgery*, 1987	ICU	US	Prospective	12	Sepsis
De Backer[26]	*Critical Care Medicine*, 1993	ICU	Belgium	Prospective	17	Sepsis
Duff[27]	*Surgery, Gynecology and Obstetrics*, 1969	NR	Canada	Prospective	21	Sepsis
Finley[28]	*Surgery*, 1975	NR	Canada	Prospective	7	Sepsis
Jardin[29]	*Critical Care Medicine*, 1979	ICU	France	Prospective	25	Severe sepsis
Kwaan[30]	*Surgery, Gynecology and Obstetrics*, 1969	Shock unit	US	Retrospective	14	Sepsis
Lee[31]	*Anesthesiology*, 1972	ICU	US	Prospective	7	Septic shock
MacLean[32]	*Annals of Surgery*, 1967	ICU	Canada	Prospective	56	Septic shock
Mitsuo[33]	*Critical Care Medicine*, 1992	ICU	Japan	Prospective	10	Sepsis
Morton[34]	*Anaesthesia and Intensive Care*, 1975	ICU	Australia	Retrospective	4	Septic shock
Motsay[35]	*Surgery*, 1970	Shock unit	US	Retrospective	15	Septic shock
Rackow[36]	*Circulatory Shock*, 1987	ICU	US	Prospective	18	Septic shock
Rackow[37]	*Critical Care Medicine*, 1989	ICU	US	Prospective	20	Severe sepsis
Shoemaker[38]	*Archives of Surgery*, 1966	Ward	US	Retrospective	10	Septic shock
Shoemaker[39]	*Chest*, 1993	Shock unit	US	Prospective	54	Septic shock
Troskot[40]	*Croatian Medical Journal*, 2010	ICU	Croatia	Prospective	31	Severe sepsis, septic shock
Tuchschmidt[41]	*Critical Care Medicine*, 1989	ICU	US	Retrospective	78	Septic shock
Udhoji[42]	*American Journal of Medicine*, 1963	Ward	US	Prospective	5	Septic shock
Villazon[7]	*Critical Care Medicine*, 1975	ICU	Mexico	Retrospective	29	Sepsis
Werdan[43]	*Clinical Research in Cardiology*, 2011	ICU	Germany	Prospective	24	Severe sepsis
Wilhelm[44]	*Clinical Research in Cardiology*, 2013	ED	Germany	Prospective	141	Sepsis, severe sepsis, septic shock
Wilson[45]	*Archives of Surgery*, 1965	Shock unit	US	Prospective	12	Septic shock
Winslow[46]	*American Journal of Medicine*, 1973	ICU	US	Prospective	50	Septic shock

ICU = intensive care unit. US = United States. NR = not reported. ED = emergency department.

Figure 2. Cardiac index (CI) and heart rate (HR) in studies with possibly and likely true native cardiac output in sepsis

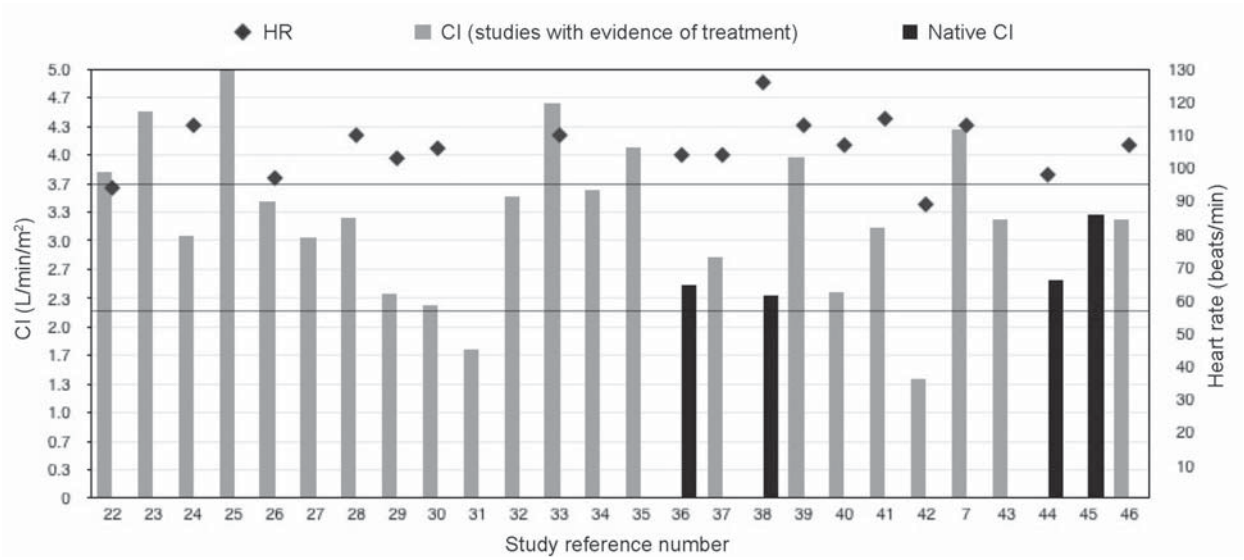


Table 3. Studies in which cardiac output was not measured at onset of sepsis or was measured after treatment was initiated

First author	Year	Time of CO measurement	Comments
Berre[22]	1997	After a stable period of 2 h	Excluded unstable patients
Castagneto[23]	1983	Reported mean CO over 6 days	CO at onset of sepsis not reported
Clowes[24]	1978	At time of blood sampling	18 patients (47%) received glucose infusions before study
Dahn[25]	1987	After > 24 h, daily between 9 and 10 am	CO not measured at onset of sepsis
De Backer[26]	1993	Before and after study drug	Comorbidities suggest prior fluid therapy (pancreatitis, crush syndrome, abdominal aortic aneurysm, trauma)
Duff[27]	1969	NR	Patients possibly treated with isoproterenol and phenoxybenzamine
Finley[28]	1975	NR	–
Kwaan[30]	1969	NR	–
Lee[31]	1972	After intubation	Sodium bicarbonate given before study
MacLean[32]	1967	Within 2 h of shock	CO measured after initiating treatment in some patients
Mitsuo[33]	1992	Within 24 h of diagnosis	CO at onset of sepsis not reported
Morton[34]	1975	NR	CO not measured at onset of sepsis
Motsay[35]	1970	Within 2 h of onset of shock	Treated on ward with mobile shock cart
Shoemaker[39]	1993	During stable period	Patients received "appropriate supportive therapy"
Troskot[40]	2010	At ICU admission	CO at onset of sepsis not reported
Tuchschmidt[41]	1989	NR	–
Udhoji[42]	1963	30 min after vasopressor discontinuation	CO not measured at onset of sepsis
Villazon[7]	1975	NR	–
Werdan[43]	2011	After 24 h in ICU	CO not measured at onset of sepsis
Winslow[46]	1973	Before treatment	Plasma volume expansion on ward before study very probable

CO = cardiac output. NR = not reported. ICU = intensive care unit.

Table 4. Studies with likely native cardiac output measurement

Author, year	Patients, *n*	CO measurement method	Mean age, years	CI, L/min/m²	MAP, mmHg	HR, bpm	CVP, mmHg	SVR, d x s/cm⁵*	Temp, °C	Lac, mmol/L	CPI, W/m²	SV, mL	SVI, mL	LVSWI, g/m²
Rackow, 1987[36]	18	PAC	76	2.49	61	104	5.7	1136.0	38.2	5.9	NR	NR	25.4	18.8
Shoemaker, 1966[38]	10	Indocyanine	NR	2.36	62	126	3.5	1176.0	NR	NR	NR	37	NR	NR
Wilhelm, 2013[44]	141	PAC, PiCCO, Vigileo, BI	68	2.55	87	98	NR	NR	38.2	NR	0.48	NR	NR	NR
Wilson, 1965[45]	12	Indocyanine	NR	3.30	51	NR	NR	599.0	38.3	NR	NR	NR	NR	NR

CO = cardiac output. CI = cardiac index. MAP = mean arterial pressure. HR = heart rate. bpm = beats per minute. CVP = central venous pressure. SVR = systemic vascular resistance. Temp = temperature. Lac = lactate level. CPI = cardiac power index. SV = stroke volume. SVI = stroke volume index. LVSWI = left ventricular stroke work index. PAC = pulmonary artery catheter. NR = not reported. PiCCO = pulse index continuous cardiac output. BI = bioimpedance. * Dynes x s/cm⁵.

patients were treated before haemodynamic measurement. According to the authors, the haemodynamic studies were performed whenever possible before therapy was started and while the patient was not receiving vasopressors.

Wilhelm and colleagues studied 141 patients presenting to the emergency department (ED) with sepsis, severe sepsis and septic shock.[44] CO was measured using various different technologies (transthoracic bioimpedance in 59% of patients, uncalibrated pulse contour method in 27%, calibrated pulse contour method in 9% and pulmonary artery catheter in 6%). Baseline haemodynamic data were collected soon after admission to the ED, so we could not exclude the possibility that some of these patients were treated before the measurements (we repeatedly contacted the authors but received no response). The median CI for patients with sepsis (n = 67) was 2.5 L/min/m² (IQR, 2.1–

3.0 L/min/m^2); for patients with severe sepsis (n = 47), it was 2.6 L/min/m^2 (IQR, 1.8–3.1 L/min/m^2); and for patients with septic shock (n = 27), it was 2.6 L/min/m^2 (IQR, 2.1–3.7 L/min/m^2). The reported IQRs suggest that at least 35 patients (25%) were hypodynamic and at least six patients (5%) were hyperdynamic. Overall, the cardiac power index was found to be low, with median values of 0.5 W/m^2 (IQR, 0.41–0.66 W/m^2) for sepsis, 0.47 W/m^2 (IQR, 0.36–0.62 W/m^2) for severe sepsis and 0.43 W/m^2 (IQR, 0.33–0.73 W/m^2) for septic shock.

Rackow and colleagues assessed the haemodynamics in 18 patients with septic shock before and after fluid administration.[36] The mean CI before resuscitation was 2.49 L/min/m^2 (SD, 0.8 L/min/m^2); five patients (28%) were hypodynamic and two patients (11%) were hyperdynamic. Stroke volume index (mean, 25.4 mL/m^2; SD, 10.6 mL/m^2) and left ventricular stroke work index (mean, 18.8 g/m^2; SD, 8.9 g/m^2) were significantly lower than normal.

Discussion

Key findings

We performed a systematic review of the literature to determine the initial native COs of patients presenting to hospital with severe sepsis or septic shock. Of more than 5000 studies published in the past century, the authors of only four appeared to have assessed the CO before treatment. The CIs we found in these studies, which enrolled 181 patients in total, were consistent with a normodynamic state. Three out of four studies also reported evidence of reduced cardiac performance in the earliest stage of sepsis.

Relationship to previous studies

To our knowledge, ours is the first systematic review of CO data gathered from studies examining patient parameters measured before interventions for sepsis. Several studies from the 1960s and 1970s have frequently been cited to support the concept of sepsis as a hyperdynamic cardiovascular condition, but some studies did not report the baseline CO,[10,39] were retrospective[30,34,35,41] or studied patients after several hours and after interventions.[25,34] None of these, therefore, provided information on the native CO and, because aggressive fluid resuscitation has been shown to decrease systemic vascular resistance,[47,48] the frequently observed hyperdynamic state[3] may be partly iatrogenic.

Early administration of antibiotics, intravenous fluids and vasopressors is part of the current and previous sepsis guidelines.[12] These interventions are often started before ICU admission and invasive haemodynamic monitoring. Therefore, haemodynamic studies of patients with sepsis often reflect the combined effect of the disease process and its treatment, rather than the initial cardiovascular state itself. Transthoracic echocardiography provides a rapid and non-invasive determination of CO. We found only one study that explicitly measured the CI of patients with sepsis using transthoracic echocardiography before treatment. Fang and colleagues[49] studied 94 patients with sepsis in the ED before fluid or vasopressor administration, but included data from children (age range, 5–83 years), so we excluded it from our analysis after unsuccessful attempts to obtain the data for adults. However, it is unlikely that the findings by Fang and colleagues would have altered our conclusions because they found a mean CI of 3.29 L/min/m^2 (SD, 0.8 L/min/m^2), which was also a normal CO for the age group we studied (mean age, 43 years).

Implications of study findings

Our study shows that there is a paucity of data on the native CO of patients with sepsis before resuscitation. Within the limitations of what is available, our findings suggest that the native CO in human sepsis may be within the normal range. Heart rate was consistently elevated at the onset of sepsis,[36,38,44] so a normal CO implies that stroke volume must have been low in most of the patients. Whether this is mainly due to depletion in the effective circulatory volume[50] or frankly impaired myocardial contractility[51] remains unknown.

Therefore, early bedside echocardiographic assessment is advisable, as clinicians may not have enough information about the initial CO and the possible contributors to hypotension in patients with sepsis.

Our findings also imply that our current early resuscitation constructs are not based on sufficiently robust physiological evidence. Importantly, we found no studies that convincingly supported the concept of a hyperdynamic circulation in sepsis before resuscitation. Finally, the lack of evidence supporting the benefits of inducing an iatrogenic hyperdynamic state, and the failure of early goal-directed therapy[15-17] to improve outcomes, suggests that the rationale for proposed aggressive fluid resuscitation protocols[52] is open to challenge.

Strengths and limitations

Our review has several strengths. First, to our knowledge, no other investigators have tackled the important area of haemodynamics in sepsis. Second, by using wide search criteria, we assessed a large body of literature, making it unlikely that any relevant data were missed. Third, the use of three electronic databases and additional hand searching of the literature without time limits allowed us to explore datasets across a wide time span.

Our review also has some weaknesses, in that we excluded studies that reported non-indexed CO values (10 studies with 297 patients) or graphic data only (seven studies with

257 patients). Although this may have biased our results, a reliable comparison and statistical analysis of data would not have been possible using crude CO data or approximate numbers. In addition, all these studies appeared to have been conducted after interventions had been applied. We focused on the initial CO at presentation and therefore did not analyse the effect of fluids and vasopressors, other than noting their administration. Other confounding factors that may have affected the physiological response include the duration of shock, severity of disease, clinical context and comorbidities.[38] Our study was therefore specifically directed at establishing the haemodynamic state at onset of sepsis and before therapeutic interventions.

We cannot prove that the measurements reported in the selected studies were truly obtained before any pharmacological or fluid-related intervention. However, if all the data reported as possibly representing true native values were also affected by interventions, our findings that we know little on the native CO in patients with sepsis become even more compelling.

Finally, the generalisability of our results is limited because most of the data included in our final analysis came from a single study,[44] which used four different technologies to measure CO and reported a pre-resuscitation MAP of 87 mmHg.

Conclusions

Overall, data about the initial haemodynamic presentation of patients with sepsis are scant. The limited data available suggest that a normodynamic state may be the norm in non-resuscitated patients with sepsis, and that a hypodynamic state may be more common than a hyperdynamic state. Importantly, cardiac performance seems to be impaired at the earliest stage of human sepsis, and data on the adequacy of that impaired CO for meeting metabolic demand are almost absent. As current initial resuscitation paradigms in sepsis are predicated on assumptions about the underlying pathophysiology, our findings suggest a strong need to address this knowledge deficit in the management of patients with severe sepsis.

Competing interests

None declared.

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Appendix. Methods and interventional and haemodynamic features of studies with possibly native cardiac output measurements

First author, year	CO measurement method	Patients, *n*	MV, %	Age, years	Mortality, %	IV fluids	Vasoactive drugs	CI, L/min/m²	MAP, mmHg	HR, bpm
Berre, 1997[22]	PAC	14	100	61	57	NR	N	3.8	77	94
Castagneto, 1983[23]	Fick	36	0	NR	NR	NR	NR	4.5	NR	NR
Clowes, 1978[24]	PAC, indocyanine	38	NR	53.5	54	NR	NR	3.05	75	113
Dahn, 1987[25]	Indocyanine	12	92	59	NR	NR	NR	4.98	NR	NR
De Backer, 1993[26]	PAC	17	65	63.9	47	NR	N	3.46	91	97
Duff, 1969[27]	Fick	21	NR	57	91	NR	NR	3.03	NR	NR
Finley, 1975[28]	Fick	7	NR	47	71	NR	NR	3.26	82	110
Jardin, 1979[29]	PAC	25	100	NR	NR	N	N	2.38	58	103
Kwaan, 1969[30]	Indocyanine	14	NR	61.5	65	NR	NR	2.26	NR	106
Lee, 1972[31]	Indocyanine	7	100	59	NR	N	N	1.74	NR	NR
MacLean, 1967[32]	Indocyanine	56	NR	NR	62	NR	N	3.51	NR	NR
Mitsuo, 1992[33]	PAC	10	0	40.3	50	NR	N	4.6	83	110
Morton, 1975[34]	NR	4	NR	54	50	NR	NR	3.6	NR	NR
Motsay, 1970[35]	Indocyanine	15	NR	47.7	13	N	N	4.08	NR	NR
Rackow, 1987[36]	PAC	18	NR	76	61	N	N	2.49	61	104
Rackow, 1989[37]	PAC	20	70	75	50	N	N	2.8	62	104
Shoemaker, 1966[38]	Indocyanine	10	NR	NR	40	N	N	2.36	62	126
Shoemaker, 1993[39]	PAC	54	NR	NR	52	NR	NR	3.97	83	113
Troskot, 2010[40]	PAC	31	0	67	35	NR	NR	2.4	81	107
Tuchschmidt, 1989[41]	PAC	78	NR	48	49	NR	NR	3.15	80	115
Udhoji, 1963[42]	Indocyanine	5	NR	67.8	NR	NR	N	1.4	67	89
Villazon, 1975[7]	Indocyanine	29	NR	57	NR	NR	NR	4.3	79	113
Werdan, 2011[43]	PAC	24	100	64	67	NR	NR	3.24	NR	NR
Wilhelm, 2013[44]	PAC, PiCCO, Vigileo, BI	141	NR	68	12	NR	NR	2.55	87	98
Wilson, 1965[45]	Indocyanine	12	NR	NR	50	N	N	3.3	51	NR
Winslow, 1973[46]	Indocyanine	50	NR	62.8	92	N	N	3.24	55	107

CO = cardiac output. MV = mechanical ventilation. IV = intravenous. CI = cardiac index. MAP = mean arterial pressure. HR = heart rate. bpm = beats per minute. PAC = pulmonary artery catheter. NR = not reported. N = no. PiCCO = pulse index continuous cardiac output. BI = bioimpedance.