British Journal of Medicine & Medical Research
5(4): 427-433, 2015, Article no.BJMMR.2015.047
ISSN: 2231-0614

SCIENCEDOMAIN *international*
www.sciencedomain.org

Cardiac Dysfunction in Patients with Sepsis, Severe Sepsis and Septic Shock

Tom Devasia[1*], Hashir Kareem[1], Y. G. Ashok Kumar[2], R. Padma Kumar[1], Saumya Jose[1], Sharmila Sadanand Prabhu[3], Umesh Pai[4], Krishnanand Nayak[1], Tulsee Sitapara[5] and Ashok Thakkar[5]

[1]Department of Cardiology, Kasturba Medical College and Hospital, Manipal - 576104, Karnataka, India.
[2]Department of Medicine, Srinivas Medical College, Srinivas Nagar, Mukka, Surathkal, Mangalore - 575 021, Karnataka, India.
[3]SOAHS, Kasturba Medical College and Hospital, Manipal - 576104, Karnataka, India.
[4]MCOAHS, Kasturba Medical College and Hospital, Manipal - 576104, Karnataka, India.
[5]Department of Clinical Trials, Sahajanand Medical Technologies Pvt. Ltd., Surat - 395004, Gujarat, India.

Authors' contributions

Authors TD, HK, YGAK, SSP, SJ, KN and PKR conducted the study. Author UP assisted in study design and data collection. Authors TS and AT were involved in technical writing and manuscript preparation. All authors read and approved the final manuscript.

Article Information

DOI:10.9734/BJMMR/2015/12334
Editor(s):
(1) Gaetano Santulli, College of Physicians and Surgeons Columbia University Medical Center, New York, NY, USA.
Reviewers:
(1) Salah A.M. Said, Clinical cardiologist, Hospital Group Twente, The Netherlands.
(2) Anonymous, Federal University of Rio Grande do Norte, Brazil.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=663&id=12&aid=6113

Original Research Article

Received 27th June 2014
Accepted 22nd July 2014
Published 16th September 2014

ABSTRACT

Aims: Patients with severe sepsis and septic shock often exhibit significant cardiovascular dysfunction. We designed the study with an aim to determine the severity of cardiac dysfunction in the different group of sepsis patients.
Study Design: Single-center, cross-sectional study
Place and Duration of Study: The study was carried out at Department of Cardiology, Kasturba Medical College and Hospital, Manipal from June 2011 to December 2012.
Methodology: A total of 74 patients who were diagnosed with sepsis were enrolled in the study. All patients were subjected to routine analysis, laboratory test and echocardiogrphic assessment.
Results: The patients were divided into 3 groups: sepsis group (n = 11), severe sepsis group (n =

**Corresponding author: Email: tomdevasia@hotmail.com;*

37) and septic shock group (n = 26). The mitral E/A value is significantly higher in patients with septic shock than that of the patients with sepsis (P = 0.04). The indices of right ventricular dysfunction did not show any significant difference in the patients with septic shock and that of sepsis.

Conclusion: Left ventricular dysfunction may be considered prevalent in sepsis as per the significant E/A values. However, the other echocardiographic parameter should also be considered. This may even infer that cardiac dysfunction may not correlate with the severity of sepsis.

Keywords: Cardiac dysfunction; septic shock; sepsis; severe sepsis; echocardiography.

ABBREVIATIONS

RV - Right ventricle; LV - Left ventricle; ECG – Electrocardiogram; TLC – Total leukocyte count; EF – Ejection fraction; E' – Early mitral annular velocity; A' – Late mitral annular velocity; S' – Systolic mitral annular velocity; E - Early mitral velocity; A - Late mitral velocity; IVCT – Isovolumic contraction time; IVRT – Isovolumic relaxation time; ET – Ejection time; MPI – Myocardial performance index; LVEDD – Left ventricular end diastolic dimension; TAPSE – Tricuspid annular plane systolic excursion.

1. INTRODUCTION

Sepsis and septic shock are severe health problems associated with higher mortality and morbidity [1]. The frequency of hospitalization and morbidity in severely ill patients with sepsis is increasing, with mortality rates as high as 70% [2,3]. Multiple mechanisms seem to be involved in the sepsis, including myocardial performance [4].

Cardiovascular disease has become one of the major causes of death accounting up to 30% [5]. The entire cardiovascular system is involved in the pathophysiology of severe sepsis and septic shock [6]. Myocardial dysfunction is a common complication [7] among patients with severe sepsis and its early detection and aggressive supportive treatment are mandatory due to their high incidence of fatality [8].

The underlying mechanisms involved in the development of myocardial dysfunction during sepsis are not entirely known but involve circulating factors, such as tumor necrosis factor α and interleukin 1 β, production of reactive free radicals and oxidants, activation of toll-like receptors, cardiomyocyte apoptosis, and endothelial dysfunction [9,10].

A tissue Doppler imaging is an echocardiography technique which is also superior to conventional echocardiography in terms of assessing systolic and diastolic dysfunction. Most research on cardiovascular dysfunction in septic patients has focused on diastolic dysfunctions and systolic dysfunction separately [11-14].

Limited data were observed regarding cardiac dysfunction in septicemia patients in India. Due to the paucity of results, we carried out the study in rural area of India with an aim to analyze the importance of LV (left ventricular) and RV (right ventricular) dysfunction in patients presenting sepsis, severe sepsis and septic shock using tissue Doppler echocardiography.

2. METHODOLOGY

2.1 Study Design

This single-center and cross-sectional study was carried out at Kasturba Medical College and Hospital, Manipal from June 2011 to December 2012.

2.2 Study Methods

In this study, a total of 74 patients who were diagnosed with sepsis were enrolled in the study. According to ACCP/SCCM (American College of Chest Physicians/Society of Critical Care Medicine) Consensus Conference Committee of sepsis [15], patients were divided into 3 categories which are represented in Table 1.

All patients older than 18 years and who consulted to the Cardiology Department of the hospital were included in the study. Patients having known ischemic heart disease, dilated cardiomyopathy, valvular heart diseases, connective tissue disorder, and arrhythmias were excluded from the study.

Table 1. Classification of sepsis according to ACC/AHA guidelines

Condition	Description
Sepsis	The presence of infection, documented or strongly suspected, with a systemic inflammatory response, together with two or more of the following: -Temperature > 38 °C or < 36°C -Heart Rate > 90 bpm -Respiratory Rate (RR) 30/min with $PaCO_2$ < 32 - TLC (Total Leukocyte Count) > 12×10^9 /L or < 4×10^9 /L or > 10% staff cells together with, septic shock (sepsis induced tissue hypoperfusion or organ dysfunction
Severe sepsis	Sepsis complicated by organ dysfunction or organ hypoperfusion.
Septic shock	Severe sepsis complicated by acute circulatory failure characterized by persistent arterial hypotension (defined as a systolic arterial blood pressure < 90 mm Hg or reduction from baseline by > 40 mm Hg), despite adequate volume resuscitation, and unexplained by both

The patients were observed clinically. All patients were subjected to base line 12-lead ECG (electrocardiogram), tissue Doppler echocardiography and routine laboratory tests.

2.3 Echocardiography

All patients underwent 12 lead electrocardiogram and echocardiography using vivid e portable Echo machine from GE health care using 2.5 MHz transducer and Doppler echocardiography including Tissue Doppler Imaging. Left decubitis position was used to analyze the patients. Two dimensional imaging examinations were performed in the standard apical four and two chamber views which enhance the image quality. Assessments were made using parasternal long axis, short axis, apical four chamber and two chamber images according to the American Echocardiography Association Criteria. The LV end diastolic volumes and the end systolic volumes were measured in the apical 4 chamber view.

The sample was placed on the RV-free wall at 1 cm apical to the tricuspid annulus in the apical four chamber imaging. For LV assessment, the sample was placed on lateral, septal, anterior and posterior LV wall in various echocardiographic views. Using TDI (tissue Doppler imaging) recordings, following measurements were calculated in apical four chamber view: (E') Early, (A') late diastolic velocities, and (S') Myocardial peak systolic, IVCT (Isovolumic contraction time), IVRT (isovolumic relaxation time), ET (ejection time) and MPI (myocardial performance index).The patients depicted good quality images. The IVCT was defined as the time from the closure of mitral valve to onset of LV ejection. IVRT was defined as the time from closure of aortic valve to onset of filling by opening of mitral valve. The ET was defined as the time period from the opening to the closing of the aortic valve. The MPI was calculated using the following equation: ([IVCT + IVRT]/ET). The recordings of three consecutive cardiac cycles with simultaneous electrocardiography were used to obtain an average value. The TAPSE (tricuspid annular plane systolic excursion) was also measured.

2.4 Statistical Data

Data were collected and coded prior to analysis using SPSS (Statistical Package for Social Sciences) version 15. Normality among the data was observed using Kolmogrov Smirnov test. Continuous data are expressed as mean ± standard deviation (SD). Categorical data are presented as number of patients (percentage). The differences among 3 groups were analyzed by using the Kruskall - Wallis for the non parametric data.

3. RESULTS AND DISCUSSION

3.1 Results

This study included 74 patients (34 males), aged 50.38 ± 16.11 years, who were diagnosed with various degrees of systemic sepsis. (Table 2) shows the baseline demographic and echocardiographic characteristic of these patients. The patients were divided into three groups according to the severity of sepsis: sepsis (11 patients), severe sepsis (37 patients) and septic shock (26 patients).

Table 2. Comparison of baseline and echocardiographic characteristics between patients with sepsis, severe sepsis and septic shock

Variables	Sepsis (n=11)	Severe sepsis (n=37)	Septic shock (n=26)	P value
Demographic parameters				
Age (years)	48 ± 14.3	52.4 ± 15.7	48.4 ± 17.7	0.555
Gender				
Male, n (%)	7 (63.6)	17 (45.9)	10 (38.5)	0.416
Social history				
Alcoholic, n (%)	0 (0)	4 (10.8)	0 (0)	0.198
Smoker, n (%)	0 (0)	4 (10.8)	1 (3.8)	0.450
Co morbidities				
Diabetes Mellitus, n (%)	0 (0)	1 (2.7)	3 (11.5)	0.356
Hypertension, n (%)	0 (0)	2 (5.4)	1 (3.8)	1.00
COPD, n (%)	0 (0)	7 (18.9)	0 (0)	0.384
CKD, n (%)	1 (9.1)	14 (37.8)	12 (46.1)	0.104
Clinical data				
Pulse rate (beat/min)	111.2 ± 15.2	108.2 ± 14.8	113.5 ± 19.7	0.930
Fever (° F)	95.8 ± 11.5	99.5 ± 8.7	100.5 ± 10	0.377
Mean blood pressure (mm Hg)	81.1 ± 8.9	83.9 ± 10.9	77.7 ± 11.1	0.666
Respiratory rate (breath/min)	24.4 ± 2.8	22.2 ± 4.2	24.9 ± 7.6	0.957
Laboratory parameters				
Hemoglobin (gm/dL)	11 ± 1.4	11.3 ± 2.2	11.56 ± 2.22	0.778
Total leukocytic count (× 10^9/ L)	15.3 ± 8.6	16.8 ± 11.1	17.8 ± 24.3	0.904
Serum creatinine (mg/dL)	1.1 ± 0.3	1.7 ± 1.5	1.8 ± 1.6	0.320
Blood urea nitrogen (mg/dL)	44 ± 36.9	73.6 ± 63.9	57.8 ± 37.8	0.745
Total bilirubin (mg/dL)	1.2 ± 0.8	4.1 ± 7.6	2.41 ± 2.25	0.810
AST (IU/L)	122.7 ± 69.8	217.1 ± 357.7	166.6 ± 267.7	0.914
ALP (IU/L)	201.5 ± 79	221.8 ± 183.5	180.9 ± 17.1	0.921
pH	7.1 ± 0.1	7.1 ± 0.2	7.27 ± 0.16	0.036
Echocardiography data LV dysfunction				
Left Ventricular End Diastolic Dimension (mm)	45.5 ± 5.8	45.6 ± 5.8	45.5 ± 6.6	0.990
Left Ventricular End Systolic Dimension (mm)	28.9 ± 6.1	29 ± 6.4	30.9 ± 7.8	0.626
Ejection fraction (%)	61.7 ± 15	60.1 ± 9.5	56.9 ± 13.2	0.168
Fractional shortening (mm)	34 ± 9.6	31.8 ± 6.2	30.26 ± 7.8	0.131
Mitral E/ Septal E'	0.087 ± 0.02	0.09 ± 0.02	0.086 ± 0.02	0.847
Mitral E/A	1.3 ± 0.51	1.2 ± 0.42	1.5 ± 0.6	0.041
S' (cm/s)	10.81 ± 3.02	9.3 ± 3.6	9.3 ± 3.28	0.939
Interventricular septal E'/A'	1.26 ± 0.43	1.3 ± 0.52	1.37 ± 0.46	0.683
LV performance index	0.38 ± 0.048	0.407 ± 0.08	0.4 ± 0.16	0.520
RV dysfunction				
TAPSE	24.2 ± 3.8	21.9 ± 3.4	21.69 ± 3.8	0.111
RV performance index	0.36 ± 0.54	0.35 ± 0.02	0.38 ± 0.076	0.490

CKD: Chronic kidney disease, COPD: chronic obstructive pulmonary disease, AST: aspartate amino transferase, ALP: alkaline phosphatase, LV: left ventricular, E: early mitral velocity, E': early mitral annular velocity, A: late mitral velocity, S': mitral annular velocity at systole, RV: right ventricle, TAPSE: tricuspid annular plane systolic excursion. Data is represented as mean ± SD

Among the patients with sepsis, neither patient was found alcoholic or smoker. Four patients among the severe sepsis group were alcoholic and four were even smoker (one among them had both habits).Chronic kidney disease was common co-morbidity in sepsis patients with 9.1%, 37.8% and 46.1% in sepsis, severe sepsis and septic shock patients respectively. Various laboratory data like total leukocyte count, aspartate amino transferase, serum creatinine were found higher in septic shock patients but not statistically significant. Only the significant

difference between groups was observed among the pH (*P* = .036).

Among the 74 patients, 17 (22.97%) had LVEF of ≤ 50% and 22 (29.72%) had septal E' velocity of < 8cm/s. Among the patients with septic shock, 7 patients had (3.86%) LVEF of ≤ 50% and 7 (3.86%) had septal E' velocity of < 8cm/s. Among the indices of LV dysfunction, E/A ratio depicted a significant difference among the septic shock patients *(P = .04)*. There was no significant difference between the groups in terms of LVEDD (LV-end diastolic dysfunction), LVESD (left ventricular systolic dysfunction), ejection fraction, and mitral E velocity/ septal E' velocity. The fractional shortening was found to be low in patients with septic shock as compared to sepsis patients but was not significantly different. The LV-MPI was comparatively high in both the severe sepsis and septic shock group than normal, but no significant difference was observed among them.

None of the indices of RV dysfunction represented significant difference among the sepsis and septic shock patients.

3.2 Discussion

Sepsis is the most important cause of death among critically ill patients. Echocardiographic studies have reported impaired LV systolic and diastolic function in septic patients [16-18]. Apart from human studies, experimental studies ranging from the cellular level [19] to heart studies [20] and to in vivo animal models [21,22] established decreased contractility and impaired myocardial compliance as major factors that cause myocardial dysfunction in sepsis. There are numerous mechanisms underlying the cardiac dysfunction in sepsis. A dose-dependent effect on cardiovascular risk was exerted by continuous variables such as blood pressure, plasma glucose, and lipids [23].

Assessment of diastolic function is carried out by different echocardiographic measurements including the ratio of E/A velocities (early mitral velocity to late mitral velocity), deceleration time, ratio of E'/A' on tissue Doppler imaging and pulmonary venous velocities [24]. Our study observed a statistical difference in E/A ratio among septic shock patients. This may be a considerable parameter for diagnosing diastolic dysfunction in sepsis patients, however still the other parameters should be taken into account.

The present study did not show any statistical significance among laboratory parameters between sepsis and septic shock patients. Comparing the mean laboratory values of sepsis and septic shock, total leukocyte counts, serum creatinine, blood urea nitrogen, total bilirubin and aspartate amino transaminase showed increased values in septic shock patients.

In septic shock patients, LV end diastolic dimension value was almost similar in all the groups which were in contrast to reported results [25,26] Lower ejection fraction mean values were observed in septic shock patients which was found alike to the study carried out by Harmankaya and colleagues [13] but was observed in disparity with the studies reported by Parker et al. [27] and others [14,25].

Among the indices of right ventricular dysfunction in patients with septic shock, TAPSE and s' mean values show minimal depression than in patients with sepsis (but statistically insignificant). No statistical significance was observed in the indices of right ventricular dysfunction among the patients with sepsis and septic shock. The MPI index obtained from cardiac time interval analysis provides information about the systolic and diastolic functions of the ventricle [28,29]. This may confer that the right ventricular dysfunction is not related to the severity of sepsis.

The findings of this studies are in congruent with the other studies reporting the LV dysfunction in sepsis [30,31]. This may depict that there is independent co-relation between the myocardial involvement (by echocardiography) and sepsis. This even infers that the severity of sepsis is not related to the echocardiographic myocardial involvement i.e., across all grades of severity of sepsis, the cardiac involvement is similar.

4. CONCLUSION

In a gist, cardiac dysfunction is an independent predictor in the septic patients. As only E/A ratio shows statistical significance among the echocardiographic parameters, the relation between severity of sepsis and cardiac dysfunction is vague. Due to continually changing physiologic profile of the patients with severe sepsis and septic shock, the clinical importance of this finding is unclear.

CONSENT

Informed consent was obtained from the patients or if not possible, from the next of kin.

ETHICAL APPROVAL

The study was approved by institutional ethics committee of the hospital and has therefore been performed in accordance with the ethical standards laid down in the 1964 declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Kumar A, Parrillo JE, Kumar A. Clinical review: Myocardial depression in sepsis and septic shock. Critical Care. 2002;6(6):500.
2. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Critical care medicine. 2007;35(5):1244-50. doi-10.1097/01.ccm.0000261890.41311.e9
3. Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Occurrence and outcomes of sepsis: influence of race. Critical care medicine. 2007;35(3):763-8. doi-10.1097/01.ccm.0000256726.80998.bf
4. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock. Critical Care Clinics. 2000;16(2):251-87.
5. Santulli G. Epidemiology of cardiovascular disease in the 21st century: updated numbers and updated facts. Journal of Cardiovascular Diseases. 2013;1(1):1-2.
6. Parrillo JE. Pathogenetic mechanisms of septic shock. The New England Journal of Medicine. 1993;328(20):1471-7. doi-10.1056/nejm199305203282008
7. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. Annals of Internal Medicine. 1984;100(4):483-90.
8. Annane D, Bellissant E, Cavaillon JM. Septic shock. Lancet. 2005;365(9453):63-78. doi-10.1016/s0140-6736(04)17667-8
9. Lorigados CB, Soriano FG, Szabo C. Pathomechanisms of myocardial dysfunction in sepsis. Endocrine, Metabolic & Immune Disorders Drug Targets. 2010;10(3):274-84.
10. Zou L, Feng Y, Chen YJ, Si R, Shen S, Zhou Q, et al. Toll-like receptor 2 plays a critical role in cardiac dysfunction during polymicrobial sepsis. Critical Care Medicine. 2010;38(5):1335-42. doi-10.1097/CCM.0b013e3181d99e67
11. Bergenzaun L, Gudmundsson P, Ohlin H, During J, Ersson A, Ihrman L, et al. Assessing left ventricular systolic function in shock: evaluation of echocardiographic parameters in intensive care. Crit Care. 2011;15(4):R200.
12. Parker M, McCarthy K, Ognibene F, Parrillo J. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. CHEST Journal. 1990;97(1):126-31.
13. Harmankaya A, Akilli H, Gul M, Akilli NB, Ergin M, Aribas A, et al. Assessment of right ventricular functions in patients with sepsis, severe sepsis and septic shock and its prognostic importance: A tissue Doppler study. Journal of Critical Care. 2013;28(6):1111. e7-. e11.
14. Brown SM, Pittman JE, Hirshberg EL, Jones JP, Lanspa MJ, Kuttler KG, et al. Diastolic dysfunction and mortality in early severe sepsis and septic shock: a prospective, observational echocardiography study. Critical Ultrasound Journal. 2012;4(1):1-9.
15. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. 1992. Chest. 2009;136(5 Suppl):e28.
16. Jafri SM, Lavine S, Field BE, Bahorozian MT, Carlson RW. Left ventricular diastolic function in sepsis. Critical Care Medicine. 1990;18(7):709-14.
17. Munt B, Jue J, Gin K, Fenwick J, Tweeddale M. Diastolic filling in human severe sepsis: an echocardiographic study. Critical Care Medicine. 1998;26(11):1829-33.
18. Poelaert J, Declerck C, Vogelaers D, Colardyn F, Visser CA. Left ventricular

systolic and diastolic function in septic shock. Intensive Care Medicine. 1997;23(5):553-60.
19. Ren J, Ren BH, Sharma AC. Sepsis-induced depressed contractile function of isolated ventricular myocytes is due to altered calcium transient properties. Shock (Augusta, Ga). 2002;18(3):285-8.
20. Merx MW, Liehn EA, Janssens U, Lutticken R, Schrader J, Hanrath P, et al. HMG-CoA reductase inhibitor simvastatin profoundly improves survival in a murine model of sepsis. Circulation. 2004;109(21):2560-5. doi-10.1161/01.cir.0000129774.09737.5b
21. Stahl TJ, Alden PB, Ring WS, Madoff RC, Cerra FB. Sepsis-induced diastolic dysfunction in chronic canine peritonitis. The American Journal of Physiology. 1990;258(3 Pt 2):H625-33.
22. Merx MW, Liehn EA, Graf J, van de Sandt A, Schaltenbrand M, Schrader J, et al. Statin treatment after onset of sepsis in a murine model improves survival. Circulation. 2005;112(1):117-24. doi-10.1161/circulationaha.104.502195
23. Santulli G. Coronary heart disease risk factors and mortality. JAMA. 2012;307(11):1137-8.
24. Hochstadt A, Meroz Y, Landesberg G. Myocardial dysfunction in severe sepsis and septic shock: more questions than answers? Journal of Cardiothoracic and Vascular Anesthesia. 2011;25(3):526-35. doi-10.1053/j.jvca.2010.11.026
25. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F. Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. American Journal of Respiratory and Critical Care Medicine. 2003;168(11):1270-6. doi-10.1164/rccm.200306-816CC
26. Jardin F, Fourme T, Page B, Loubieres Y, Vieillard-Baron A, Beauchet A, et al. Persistent preload defect in severe sepsis despite fluid loading: A longitudinal echocardiographic study in patients with septic shock. Chest. 1999;116(5):1354-9.
27. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, Frederick TM, et al. Profound but reversible myocardial depression in patients with septic shock. Annals of Internal Medicine. 1984;100(4):483-90.
28. Tei C. New non-invasive index for combined systolic and diastolic ventricular function. Journal of Cardiology. 1995;26(2):135-6.
29. Tei C, Nishimura RA, Seward JB, Tajik AJ. Noninvasive Doppler-derived myocardial performance index: correlation with simultaneous measurements of cardiac catheterization measurements. Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography. 1997;10(2):169-78.
30. Omar AA, El-Shahat N, Ramadan MM. Cardiac functions in patients with sepsis and septic shock. The Egyptian Heart Journal. 2012;64(4):191-6.
31. Landesberg G, Gilon D, Meroz Y, Georgieva M, Levin PD, Goodman S, et al. Diastolic dysfunction and mortality in severe sepsis and septic shock. European Heart Journal. 2012;33(7):895-903.

Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=663&id=12&aid=6113