Diastolic Dysfunction in Septic Patients in Correlation with Renal Function

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Abstract:: Septic shock remains one of the most challenging medical conditions, with increasing incidence over the last years. One of the most important features of sepsis is myocardial dysfunction and renal impairment. **Objective** is to evaluate diastolic dysfunction in patient with septicemia and detect its relationto renal impairment in this subset of patients. **Methods** The study was conducted on 40 patients diagnosed to have various degrees of systemic sepsis admitted to Intensive Care Unit of Mansoura International Specialized Hospital.After exclusion of patients with structural heart diseases and renal impairment, each patient was subjected to the following: Full clinical evaluation, complete laboratory investigation -including serum troponin I &creatinine levels- and echocardiographic evaluation with measuring of left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), calculation of LVEF& assessment of diastolic function measuring mitral annulus E/A ratio, E deceleration time(DT)& isovolumic relaxation time (IVRT) **Results**A non -randomized non-controlled prospective study done between July 2009 to August 2010. The study included 40 patients, 24 males & 16 females, with mean age of 62±12. Renal impairment (defined as serum creatinine > 1.4 mg/dl following a normal creatinine level on admission associated with oliguria <0.5 ml/kg/6hours)was present in 78% (31 pts). These pts had significantly shorter IVRT & shorter DT than those with normal renal function. LVEDD and LVESD were significantly larger&LVEF was significantly lower in pts with renal impairment. Renal impairment was associated with significantly lower hemoglobin, higher liver enzymes, higher bilirubin and higher troponin levels. Eighteen patients had SIRS & sepsis (group A, 45%) & 22 had septic shock (group B, 55%). Patients with septic shock showed significantly higher creatinine & significantly higher troponin level than pts with sepsis. Regarding ventricular functions, LVEDD and LVESD were significantly larger&LVEF was significantly lower in septic shock ptsthan pts with SIRS & sepsis. In group B, both DT and IVRT were significantly shorter than group A.Overallmortality was 55% (100% in septic shock versus 0% in pts with SIRS & sepsis). **Conclusion**The presence of renal impairment was associated with a more severe form of diastolic & systolic dysfunction in septic patients. Septic shock patients' showed larger ventricular dimensions and significant systolic and diastolic dysfunctions than patients with sepsis. Higher evidence of myocardial injury in septic shock.

[Sabry A. Omar, Mohamed Elshafey; Khalid Toema and Rania El-Hoseiny **Diastolic Dysfunction in Septic Patients in Correlation with Renal Function.** Life Science Journal 2012;9(1):572-579]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 85

Key Words: Diastolic dysfunction, septic patients, renal function

1. Introduction

Sepsis, defined by Consensus Conference as "the systemic inflammatory response syndrome (SIRS) that occurs during infection," is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individuals [1,2]. Although much has been learned about the pathophysiology of sepsis in the last decade, the mortality of this condition is still high.

One of the most important features of sepsis is myocardial dysfunction[3].

The hemodynamic pattern in human septic shock is generally characterized by a hypercirculatory state including decreased systemic vascular resistance and a markedly increased cardiac index after adequate fluid resuscitation[4]. Nevertheless, several studies have revealed clear evidence of intrinsic depressed left ventricular performance in patients with septic shock[5,6].

Sepsis-induced myocardial dysfunction has traditionally been thought of as principally affecting systolic heart function. One of the primary reasons for this concept is that systolic dysfunction is relatively easy to conceptualize, visualize, and measure[7]. Recently, anevidence is beginning to emerge regarding impaired cardiac relaxation in sepsis[8,9].

Acute kidney injury (AKI)approximately develops in 11%-64% of septic patients and is associated with a higher morbidity and mortality[10].

Several mechanisms have been proposed for the pathogenesis of AKI occuring in sepsis. In normal states, the kidney maintains renal blood flow and glomerular filtration through auto regulation dependant on the tone of the afferent and efferent arterioles, this auto regulation is disturbed in sepsis. The cytokines –induced systemic vasodilatation and relative hypovolaemia in sepsis are responsible for

renal hypoperfusion. The renal vasculature has been shown to participate variably to mediators of systemic vasodilatation and renal blood flow has been shown to be variable in septic models [11].

Secondary cardiorenal syndrome (CRS Type 5) is a systemic illness leading to simultaneous heart and renal failure. This is almost always in the setting of critical illness such as sepsis, multiple trauma, or burns[12].

Sepsis as a precipitator of CRS Type 5 is common and its incidence is increasing, with a mortality estimated at 20%-60%[13,14].

2. Patients and Methods:

Between July 2009 and August 2010, 40 patients diagnosed to have various degrees of systemic sepsis, Admitted to the Critical Care Unit of Mansoura International Specialized Hospital were enrolled in our study.

Inclusion Criteria:

1. SIRS defined as Two or more of the following parameters:
   - Temperature >38Cº or <36Cº.
   - HR >90 bpm
   - RR >20/min with paCO2<32 mmHg.
   - TLC >12000/dl or <4000/dl or >10% staff cells.
2. Sepsis defined as SIRS + confirmed source of infection.
3. Severe sepsis defined as sepsis with organ dysfunction, hypoperfusion, or hypotension.
4. Septic shock defined as sepsis with refractory arterial hypotension (a systolic pressure <90mmHg,or reduced from baseline by >40 mmHg) or hypoperfusion abnormalities in spite of adequate fluid resuscitation.

Exclusion criteria:

1. Patients with knownrenal impairment.
2. Patients with known structural heart disease.

The study group was subjected to:

- Full medical history.
- Baseline 12-lead ECG and daily follow up.
- Baseline arterial pressure followed by continuous monitoring of hemodynamics.
- Full blood chemistry including ;
  1. Complete blood picture
  2. Liver function tests
  3. Coagulation profile
  4. Serum troponin I
  5. Kidney function test: Urea and creatinine with value of serum creatinine > 1.4 mg/dl following a normal creatinine level on admission and oliguria is used to define impaired renal function.
- Echocardiography**:**

Each patient was subjected to 2-Dimensional, M-mode & Doppler study using ATL HDI 500 echocardiography machine using a 3.5 MHZ transducer, measuring the following parameters on admission:

1. Left ventricular end diastolic dimension (LVEDD)
2. Left ventricular end systolic dimension (LVESD)
3. Ejection fraction (EF)
4. Isovolumic relaxation time (IVRT)
5. E Deceleration time (DT)
6. E/A ratio

In our study we divided patients into two groups according to ACCP /SCCM Consensus Coference definition of sepsis;

Group A:

- Patients with SIRS & severe sepsis.
- This group included 18 patients (13 Males, 5 Females) with mean age 59.39±8.65 years.

They had adequate hemodynamic response to fluids resuscitation

Group B:

- Patients with septic shock
- This group included 22 patients (11males and 11 females) with mean age 65.05 ± 8.8 years.

They had hypotension which was not responding to fluid resuscitation and necessitate vasoactive drugs administration.

Statistical Method:

Data were collected and coded prior to analysis using the professional Statistical Package for Social Science (SPSS 10). All data were expressed as mean and standard deviation (SD). Frequency table for all categorical data .Student t- test (paired & un-paired) after checking normality for all continuous data and Standard Error (SE) of proportion was calculated AP value <0.05 was considered significant**.**

3. Results:

A non -randomized non-controlled prospective study on 40 patients diagnosed to have SIRS, sepsis & septic shock. Twenty four were males (60%) and 16 females (40%) with mean age 62± 12 years.

Eighteen patients (45%) were diabetics, and 12 (40%) had malignancy. Medical cases were 15 (38%) & surgical cases (63%). Renal impairment was diagnosed in 78% (31 patients).

Ten days mortality was 20% & overall mortality was 55% (22 pts).

Comparison between patients with normal and impaired renal function according to clinical & laboratory variables:

No age or sex difference between patients with normal & impaired renal function.

Significantly higher pulse rate, lower systolic &

diastolic BP in patients with renal impairment.

Statistically higher liver enzymes, serum bilirubin, international normalized ratio (INR), C-reactive protein (CRP) & serum troponin in patients with impaired renal function in comparison to patients with normal kidney function.

Statistically significantly lower hemoglobin (Hb) & Ca levels in patients with impaired renal functions. Table (1)

Table (1): Comparisonbetween pts with normal and impaired renal function.

Variables	Normal renal function (n=9, 22%)	Impaired renal function (n=31, 78%)	P Value
Age(Y)	56±12.1	64 ± 11.4	0.142
Gender (M)	6 (66.7 %)	18 (58.1 %)	0.16
(F)	3 (33.3 %)	13 (41.9 %)	0.18
Pulse (BPM)	107 ± 9	128 ± 12.4	0.03
SBP (mmHg)	106 ± 13.5	84.5 ± 11.2	0.005
DBP (mmHg)	57 ± 14	45 ± 11.2	0.001
TLC	20.2 ± 7	24 ± 9	0.245
HB	9.8 ± 2.4	8.45 ± 1.6	0.0174
HCT	23.3 ± 8.4	21.1 ± 10.3	0.036
Total Bil	1.14 ± 0.23	2.45 ± 1.6	0.042
SGOT	46.3 ± 22	92.4 ± 13.2	0.002
SGPT	69 ± 22	85 ± 31.4	0.03
INR	1.2 ± 0.18	2.13 ± 0.62	0.14
Urea	48.1 ± 41	87 ± 31	0.032
Creatinine	1.14 ± 0.23	2.98 ± 1.2	0.031
CR.CL	66.5 ± 28.2	32.4 ± 16.5	0.04
Calcium	9.2 ± 1.3	8.1 ± 1.3	0.09
Troponin	.045±.01590	.11585±.1160	0.035
CRP	9.8 ± 4.3	16 ± 8.5	0.0416

Comparison between patients with normal and impaired renal function according to Echocardiographic parameters.

Statistically larger EDD, ESD, and statistically lower EF inpatients with impaired renal function. Patients with impaired kidney function showed statistically shorter DT and IVRT than those with normal renal function.

No significant difference in the E/A ration between pts with normal & impaired renal function. Table (2)

Table (2):Echocardiographic parameters in patients with normal and impaired renal function.

Variables	Normal renal function (n=9, 22%)	Impaired renal function (n=31, 78%)	P Value
LVEDD	4.56 ± 0.27	5.4 ± 0.37	0.0128
LVESD	3.34 ± 0.29	3.8 ± 0.28	0.01
EF	55.2 ± 5.8	46.4 ± 2.9	0.01
IVRT	87 ± 9.2	73.2 ± 12	0.004
E/A	1.05 ± 0.14	1.36 ± 0.37	0.6
DT	231.4 ± 22.2	172 ± 32.4	0.033

Comparison between sepsis & septic shock according to clinical & laboratory data:

No age or sex difference between both groups.

Significantly higher pulse rate, lower systolic & diastolic BP in patients with septic shock.

Statistically higher liver enzymes, seum bilirubin, INR, CRP & serum troponin in group B in comparison to group A.

Statistically lower Hb level in septic shock than in sepsis. Table (3)

Table (3): Comparison between sepsis (Group A) and septic shock (Group B).

Variables	Group A (n=18, 45%)	Group B (n=22, 55%)	P Value
Age (Y)	59.39±8.6	65 ± 8	0.324
Gender (M)	13 (72 %)	11 (50 %)	0.16
(F)	5 (27 %)	11 (50 %)	0.18
Pulse (BPM)	95.6 ± 6	106.6 ± 12	0.03
SBP (mmHg)	114.7 ± 18.9	79 ± 5	0.005
DBP (mmHg)	69.4 ± 12	43 ± 7.2	0.001
TLC	16.1 ± 4	18.59 ± 4	0.115
HB	10.1 ± 1.6	9.4 ± 1.5	0.042
HCT	33.17 ± 3.5	31.27 ± 3.7	0.028
Total Bil.	1.46 ± 0.47	1.63 ± .53	0.006
SGOT	49.5 ± 14	56.23 ± 17.5	0.002
SGPT	52 ± 13	55 ± 17	0.03
INR	1.48 ± 0.58	2.42 ± 0.33	0.001
UREA	50.1 ± 20	63 ± 26	0.032
Creatinine	1.89 ± .79	2.55 ± 0.84	0.0062
CR.CL	51.6 ± 19.2	43.9 ± 18.5	0.04
Troponin	0.08818	0.11981	0.043
Calcium	8.85 ± 0.91	8.98 ± 1.05	0.075
CRP	11.78 ± 4.9	14.73 ± 4.4	0.016

Comparison between both groups according to Echocardiographic parameters:

Statistically larger EDD, ESD, and statistically lower EF inpatients with septic shock. They also showed statistically shorter DT and IVRT than those with sepsis. No significant difference in the E/A ratio between both groups. Table (4).

Table (4): Echocardiographic parameters in both groups.

parameters	Group A (n = 18)	Group B (n = 22)	P value
LVEDD (cm)	4.6 ± 0.27	5.3 ± 0.34	0.01
LVESD (cm)	3.22 ± 0.30	3.97 ± 0.27	0.018
EF (%)	56.26 ± 11.6	45.6 ± 13.5	0.01
IVRT(ms)	88. ± 8.1	74.5 ± 12	0.004
E/A ratio	0.981 ± 0.15	1.32± 0.37	0.6
DT (ms)	210.2 ± 13.2	171 ± 15.4	0.033

Mortality in both groups:

100% mortality in group B versus no mortality in group A.Eight patients (36%) died within 10 days and 14 patients (64%) died within 20 days.Table (5) & figure (1)

According to echocardiographic parameters, statistically larger LVEDD in patients died within 20 days than those who showed early mortality (LVEDD was 54.50±2.822 versus 50.88±3.227 respectively, P = 0.012). No significant difference of other echocardiographic parameters (ESD, EF, E/A ratio, DT and IVRT).

Table (5): Mortality rate in both groups.

Outcome	Group A		Group B	
	N	%	N	%
Survivors	18	100	0	0
Non-survivors	0	0	22	100

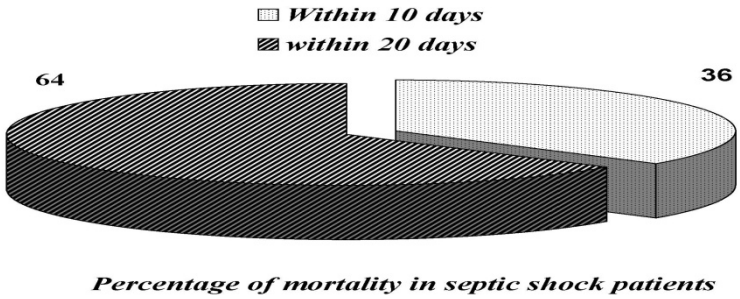

Figure (1): Percentage of mortality in septic shock patients

4. Discussion:

Sepsis is the number one cause of death among critically ill patients and accounts for more than 215,000 deaths every year in the United States alone[2,13]. Randomized controlled trials emphasizing early resuscitation have improved the prognosis of sepsis by optimizing macrocirculatory parameters[15,16]. Despite these advancements, as many as 21% to 28% of patients with severe sepsis or septic shock may die of the disease. The significant mortality that persists with maximization of global hemodynamic indices suggests that this approach may be insufficient as a total treatment strategy. Despite aggressive resuscitation, normal blood pressure, and adequate global oxygen delivery, septic patients often persist in exhibiting signs of tissue hypoperfusion, which may lead to acidosis and, ultimately, multiorgan failure [2,13,15–16].

In our study we found that patients with impaired renal function (78%, 31 patients) showed significantly decreased systolic & diastolic BP with significantly higher pulse rate than pts with normal renal functions.

These results could be explained by lower organ perfusion in this subset of patients who show more severe form of sepsis than patients with normal renal function.

Previous studies have reported that sepsis causes or contributes to AKI in 32–48% of patients[17-18]& up to 64% in septic shock alone[10].

In the PICARD study group[19], who studied 611 critically ill patients in a multicenter observational study;28% of patients had sepsis before AKI, 32% patients sepsis-free, and 40% developed sepsis 5 days after AKI diagnosis.

In the study by Bagshaw et al., [10] a total of 4,532 adult patients with septic shock were studied.64.4% of patients with septic shock developed early AKI (i.e., within 24 h after onset of hypotension). By RIFLE criteria, 16.3% had risk, 29.4% had injury and 18.7% had failure.

The difference in percentage of AKI could be explained by the different definitions of acute renal failure between studies.

Acute renal failure often accompanies sepsis due to acute tubular necrosis. The mechanism is complex but involve decrease effective intravascular volume due to systemic hypotension, direct renal vasoconstriction, release of cytokines, and activation of neutrophils by endotoxins and other peptides, which contribute to renal injury[20].

Patients with renal impairment and patients with septic shock had significantly higher liver enzymes, INR & billirubin and significantly lower Hb & Hct compared to patients with normal renal function.

These markers included higher creatinine level, liver enzymes, bilirubin & higher INR. Patients with septic shock showed lower Hb than patients with SIRS or sepsis. These parameters were comparable to the laboratory results in septic shock patients in both studies conducted by **Afifi *et al.*[21],** and **Esmat *et al.*[22],** In both studies the parameters were pointing toward more severe organ dysfunction as compared to their control groups.

Hepatic dysfunction represents a common manifestation during the sepsis process, ranging from a mild elevation of serum bilirubin and/or liver enzymes to severe hepatic failure[23]. The pathophysiology of liver injury in sepsis is multifactorial and involves infection, drugs, metabolic disturbances and a broad spectrum of inflammatory mediators[24].

In our study, troponin I was elevated in septic patients with renal impairment. In patients with severe renal dysfunction troponin T as well as troponin I, elevations are found that cannot be linked to myocardial injury. The reasons for these elevations are not yet convincingly explained. Reexpression of cardiac isoforms in skeletal muscles has been excluded by different analyses and investigators[25, 26]. Loss of membrane integrity and constant outflow from the free cytosolic troponin pool as well as amplified elevation of normal low levels because of impaired renal excretion are more likely. The higher unbound cytosolic pool and higher molecular weight

may explain why troponin T is more frequently found elevated than troponin I [27].

In asymptomatic patients with renal dysfunction, troponins are not presently part of the routine diagnostic work-up because results with regard to their predictive value based on small series was controversely discussed[27].

In the prospective landmark study by Apple et al.,[28] serum was obtained from 733 end stage renal diseade patients and measured for cardiac troponin I (cTnT) and T cTnI.

They documented 2- to 5-fold increase in all-cause mortality with increases in cTnT and cTnI in ESRD. Of particular interest is the gradual rise in risk with increasing troponin T levels independent of other variables at various discriminator levels. The level of troponins was associated with a significant increase in 1-, 2-, and 3-year mortality.

In our study, a more severe form of diastolic dysfunction was observed in patients with renal impairment. Those patients had higher LV dimensions and lower LVEF%.

The relation between cardiac & renal function in systemic illness is called the secondary cardiorenal syndrome or CRS type 5[12].

Sepsis as a precipitator of CRS Type 5 is common and its incidence is increasing, with a mortality estimated at 20%-60%[13,14]. Approximately 11%-64% of septic patients develop AKI that is associated with a higher morbidity and mortality[10]. Abnormalities in cardiac function are also common in sepsis including wall motion abnormalities and transient reductions in left ventricular ejection fraction[29]. Observational data have found approximately 30%-80% of individuals with sepsis have measurable blood troponin I or T that are above the 99th detection limits[30]. These elevated cardiac biomarkers have been associated with reduced left ventricular function and higher mortality even in patients without known coronary disease[31,32]. Importantly, volume overload as a result of aggressive fluid resuscitation appears to be a significant determinant of CRS Type 5. Among 3147 patients enrolled in the Sepsis Occurrence in Acutely Ill Patients (SOAP), there was a 36% incidence of AKI, and volume overload was the strongest predictor of mortality[31]. Iatrogenic volume overload appears to play an important additional role, possibly along passive venous congestion of the kidney, in the pathogenesis of AKI. At the same time, volume overload increases left ventricular wall tension and likely contributes to cardiac decompensation in those predisposed to both systolic and diastolic HF[32]. Cardiorenal syndrome Type 5, both AKI and markers of cardiac injury followed by volume overload are common in sepsis, with each being associated with increased mortality. However, there is a current lack of integral information on the incidence of bidirectional organ failure and its pathophysiological correlates in a variety of acute care settings[12].

In our study, as regard cardiac functions measured by echocardiography, we found that LVEDD and LVESD were significantly higher&LVEF was significantly lowerin group B (septic shock) compared to group A (sepsis or SIRS).

Reversible myocardial depression in patients with septic shock was first described in 1984 by Parker et al. using radionuclide cineangiography [5]. In a series of 20 patients, they reported a 65% incidence of left ventricular (LV) systolic dysfunction, defined by an ejection fraction <45%[5].

In 1990, using transthoracic echocardiography, Jardin et al. reported the same results [33]. The same authors published their series of 183 patients with septic shock [33-36] a hypokinetic state at admission, as defined by a low cardiac index (< 3 L/minute/m2), was present in 64 patients (35%). Assessment of LV systolic function by echocardiography found this profile associated with a markedly hypokinetic LV (mean LV ejection fraction: 38 ± 17%)

More recently, Barraud et al. confirmed the presence of severe depressed intrinsic LV contractility using LV pressure/volume loops in lipopolysaccharide-treated rabbits [37]. All of these studies, and many others demonstrate the reality of the impairment of intrinsic LV contractility in septic shock[38].

Many factors may contribute to cardiac depression during sepsis. Studies performed in humans have ruled out coronary hypoperfusion requiring coronary intervention as a cause of LV systolic dysfunction in sepsis [39, 40].

On the other hand, the role of cytokines has been strongly advocated in the genesis of septic cardiomyopathy. In 1985, Parrillo et al. demonstrated in vitro that myocardial cell shortening is reduced by exposure to the serum of septic patients [41]. Later, the same team showed that the circulating factor responsible for this was tumor necrosis factor α (TNF-α) [42], even though later studies have implicated other cytokines, such as interleukin-1β [43]. Kumar et al. suggested that the effect of cytokines on cardiac myocytes results from an increase in intracellular cGMP and in nitric oxide [44]. In addition, direct alteration in cellular respiration with mitochondrial dysfunction also was advocated [45], and, finally, Tavernier et al. suggested that increased phosphorylation of troponin I was involved by reducing myofilament response to Ca2+ [46].

In our study we found significantly highertroponin level in group B in comparison to group A. This result matched with **Arlati *et al.*,**[47],

Kristren *et al.*,[48].

In a recent large study by John et al.[49], elevated cTn I in patients with severe sepsis was associated with significantly high 28 days mortality.

In our study group B patients showed more severe form of diastolic dysfunction in the form of shorter DT & shorter IVRT E/A ration compared to patients with systemis sepsis.

These results matched with **Munt *et al.*,[50]** who measured deceleration time and E/A ratio in septic patients and they found significantly lower DT in non- survivors versus survivors while E/A ratio were lower in non-survivors (statistically not significant), and concluded that increased severity of diastolic dysfunction associated with increased mortality**.**

The severity of diastolic dysfunction in non–survivors compared to survivors could be explained by the same cause of myocardial dysfunction. The grading of diastolic dysfunction is very important in prognosis in patients with septic shock, as non-survivors showed more sever diastolic dysfunction which limited the adequate volume resuscitation which is essential for recovery in septic shock patients together with early inappropriate use of inotropic support (vasoactive drugs) in a relatively hypovolemic patients leading to increased tissue hypoperfusion and sever ischemia of vital organs[50].as they had patients with severe forms of septic shock in their study like patients of group B in our study.

In our study, 100% mortality in patients with septic shock compared to 0% mortality in sepsis and SIRS.

These results do not go with result of **Shoemaker *et al.*,[51]** who showed 71.6 % mortality, and**Vieillard *et al.*,[52]**who showed 60 % mortality in his study. Our results may be related to high degree of severity of septic shock in our subset of patients.

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2/9/2012