Reversible Impairment of Global Cardiac Function during Toxic Stage of Dengue Hemorrhagic Fever and Dengue Shock Syndrome

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Abstract

Background: The pathogenesis of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) is not entirely understood. The purpose of this study was to assess global left ventricular function in children with dengue virus infection using a myocardial performance index (MPI) also known as the Tei index. The ejection fraction (EF) was also measured.

Materials and Methods: Children with a serological or polymerase chain reaction (PCR) confirmed diagnosis of dengue virus infection was classified as dengue fever (DF), DHF or DSS according to the WHO case definition. Echocardiographic studies were performed during the febrile, toxic, convalescent stages and at follow up. To assess if myocardial injury was associated with any changes in the MPI, serum troponin T was selectively measured in 10 patients (2 DF, 6 DHF, and 2 DSS).

Results: Forty-nine patients fulfilled all the inclusion criteria. The MPI during the toxic stage was significantly higher in DSS (0.44±0.03) than DHF (0.41±0.02) than in DF group (0.34±0.02)(p = 0.015). The EF in the 3 groups and during various stages was not significantly different, although there was a trend towards a lower EF during the toxic stage in DSS (55.4±7.0) and DHF (57.7±8.6) groups than in the DF group (60.9±7.4) (p = 0.077). Serum troponin T was within normal limits in all 10 patients measured.

Conclusions: Global cardiac function in patients with dengue hemorrhagic fever and dengue shock syndrome is impaired during the toxic stage. Cardiac dysfunction was worse in patients with more severe disease.

Keywords: Dengue fever, Dengue hemorrhagic fever, Dengue shock syndrome, Cardiac function, Myocardial performance index

Introduction

Dengue virus infection is one of the most important emerging infectious diseases affecting children in tropical countries (1). Dengue hemorrhagic fever (DHF) and/or Dengue shock syndrome (DSS) occurs in some patients infected with this virus. Low cardiac output and shock are one of the most serious complications of DHF/DSS which may lead to significant morbidity or even mortality. The pathogenesis of dengue shock syndrome is still not entirely understood. Although shock in DHF / DSS has been attributed largely to decreased intravascular volume due to capillary leakage of plasma into the interstitial space (1), a few recent studies have reported impairment of cardiac function in patients with DHF/DSS (2-4). All the previous studies concentrated on impairment of left ventricular systolic function. The purpose of this study was to assess global left ventricular function in children with dengue virus infection using the myocardial performance index...
(MPI), also known as the Tei index (5). To assess any correlation between cardiac function and the severity of illness, comparisons of MPI were made between patients with dengue fever (DF), dengue hemorrhagic fever without shock (DHF) and dengue shock syndrome (DSS) during different stages of the illness. The ejection fraction was also demonstrated and contrasted with the MPI. Cardiac troponin T was measured during the toxic stage in 10 patients to ascertain if cardiac dysfunction could be a result of myocardial injury.

Methods

Study patients

Children admitted with the initial diagnosis of dengue virus infection at King Chulalongkorn Memorial Hospital, Bangkok, Thailand, during August 2002 - January 2005, were enrolled. The inclusion criteria were: 1) age 5-15 years and, 2) able to cooperate with an echocardiogram. The exclusion criteria were: 1) clinically unstable for echocardiographic study, 2) needed inotropic support, 3) had other cause(s) of cardiac dysfunction and/or other acute/chronic diseases. The progression of the patients’ illness was classified into three clinical stages as febrile, toxic and convalescent. The toxic stage was defined as the day of defervescence or the presence(s) of hemoconcentration and/or shock. The convalescent stage was defined as 24-48 hours after the toxic stage. Acute and convalescent sera were sent for serological confirmation and/or PCR in all subjects. Dengue virus infection was diagnosed and classified as DF, DHF and DSS according to the World Health Organization (WHO) case definitions (6).

All patients were treated by medical staff according to WHO guidelines (6). The research protocol was approved by the institutional ethics review committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained from an appropriate guardian and/or each patient prior to enrollment.

Echocardiography

Echocardiographic studies were performed by our investigators (A.K., S.A. or V.L.) using an Aloka Prosound SSD5500 echocardiographic machine (Aloka Inc., Tokyo, Japan) during the febrile stage, toxic stage, convalescent stage and at follow up (at least one week after discharge). Doppler measurements were performed using a standard apical 4-chamber view for mitral inflow and also a standard apical 5-chamber view for left ventricular outflow. The sample volume was positioned at the mitral valve annulus level for mitral inflow and just beyond the aortic valve for left ventricular outflow. Doppler spectral signals were recorded on video tape simultaneously with electrocardiogram and phonocardiogram and were later reviewed and measured by one investigator (P.S.) who was blinded to the clinical data of the patients, using the software provided with the echocardiographic machine. At least 6 cardiac cycles were performed for each variable and the averaged values were used. If the RR interval from the ECG varied for more than 10%, the mean RR interval was calculated and only the data points which had a RR interval of between mean ± 5 percent were used. The method of calculating MPI is shown in Figure 1.

An M-mode scan of the left ventricle obtained from a standard parasternal long-axis view, at the level of mitral valve tip was recorded on tape simultaneously with the EKG and phonocardiogram. End-diastole was defined as the time at the onset of QRS complex and end-systole was defined as the time at the first high frequency component of the second heart sound (S2) on phonocardiogram. Left ventricular volumes at end-diastole and end-systole were calculated by the method of Teichholz’s (7) and the ejection fraction was then calculated.

Confirmation of dengue virus infection

Serologic study of dengue virus infection was done at The Armed Forces Research Institute of Medical Sciences (AFRIMS, Bangkok, Thailand) using an ELISA method. The laboratory procedures and interpretations have been previously reported (8). A positive PCR test for dengue virus was accepted as an evidence of dengue virus infection in patients who did not have ELISA results due to missing specimens or due to a lack of paired specimens. Nonserotype-specific reverse transcription - nested polymerase chain reaction (RT-nested PCR) was performed at the Division of Infectious Disease, Department of Medicine, Chulalongkorn University.
School of Medicine, using consensus primers targeting 3'-untranslated region of all dengue viruses. The sensitivity and specificity of the test has been previously determined to be 86.8 and 100% using plasma or serum specimens, respectively (8).

**Determination of serum troponin T**

Serum samples of 10 patients (2 DF, 6 DHF, and 2 DSS) during the toxic stage were separated using standard laboratory procedures and stored at −70 degrees Celsius until analysis. Serum troponin T was determined at the central laboratory of Chulalongkorn hospital using the electrochemiluminescence immunoassay method (Troponin T STAT, Roche Diagnostic Inc, Mannheim, Germany). The lower limit for detection was 0.01 ng/ml. Levels above 0.01 ng/ml were considered abnormal.

**Statistics**

Data are expressed as mean ± standard deviation (SD) unless noted otherwise. One way in which ANOVA was used was to compare the difference of continuous variables between groups (DF, DHF without shock and DSS). The Chi squared test was used to compare categorical variables between the 3 groups. Statistical computation was done using commercially available statistical software (SPSS version 11, SPSS Inc, Chicago, USA). Statistical significance was defined as p<0.05.

**Results**

Forty-nine patients fulfilled all the inclusion criteria. All these patients had serological and/or PCR confirmation of dengue virus infection. The demographic and clinical data of these 49 patients are presented in Table 1.

The MPI and ejection fraction (EF) of patients with DF, DHF and DSS during the different stages of their illnesses are shown in Figure 2 (a) and 2 (b). The MPI during the toxic stage was significantly higher in DSS (0.44 ± 0.03) than in DHF (0.41 ± 0.02) or the DF group (0.34 ± 0.02) (p = 0.015) while no difference was found during the other stages of the illness. The EF in the 3 groups and during various stages was not significantly different, although there was a trend toward lower EF during the toxic stage in DSS (55.4 ± 7.0) and DHF (57.7 ± 8.6) groups than in DF group (60.9 ± 7.4) (p = 0.077).

The results of paired-t tests comparing MPI during febrile, toxic and convalescent periods with MPI during the follow up period in all patients (DF, DHF and DSS) are shown in Table 2. The MPI during the febrile stage was not different from MPI during the follow up period while an elevated MPI was seen during the toxic and convalescent stages.

Serum troponin T was not detectable (<0.01 ng/ml) in any of the tested patients (2 DF, 6 DHF and 2 DSS).
Table 1. Demographic and clinical data of 49 enrolled patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>DF (n = 17)</th>
<th>DHF (n = 23)</th>
<th>DSS (n = 9)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>10.0 0.73</td>
<td>11.2 0.58</td>
<td>11.3 1.08</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male / female)</td>
<td>9/8</td>
<td>14/9</td>
<td>6/3</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of fever before toxic stage (days)</td>
<td>4.8 0.35</td>
<td>4.6 0.21</td>
<td>4.8 0.28</td>
<td>NS</td>
</tr>
<tr>
<td>Hct maximum (%)</td>
<td>40.6 0.99</td>
<td>45 0.76</td>
<td>47.1 2.08</td>
<td>0.001</td>
</tr>
<tr>
<td>Hct minimum (%)</td>
<td>37.5 0.90</td>
<td>38.0 0.80</td>
<td>39.3 1.62</td>
<td>NS</td>
</tr>
<tr>
<td>Minimum Plt (per mm(^3))</td>
<td>85,438 ± 7,748</td>
<td>43,304 6,192</td>
<td>34,333 5,220</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Hct = hematocrit; NS = not significant; Plt = platelets

Table 2. The results of paired t-test comparing the MPI during febrile, toxic and convalescent stages with the MPI during follow up.

<table>
<thead>
<tr>
<th>Comparison Groups</th>
<th>MPI during illness</th>
<th>MPI at FU</th>
<th>n</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total: MPI febrile vs FU</td>
<td>0.31 0.02</td>
<td>0.29 0.02</td>
<td>19</td>
<td>0.16</td>
</tr>
<tr>
<td>MPI toxic vs FU</td>
<td>0.39 0.01</td>
<td>0.31 0.01</td>
<td>49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MPI conv vs FU</td>
<td>0.38 0.01</td>
<td>0.31 0.01</td>
<td>43</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Conv = convalescent stage; FU = follow up

Discussion
The pathogenesis of dengue shock syndrome is still not entirely understood. Although increased vascular permeability has been shown in patients with DHF compared to normal control, the degree of vascular permeability abnormality was not different between DHF patients with and without shock (9). In most cases of DSS, shock could be explained by plasma leakage and hemorrhage, however, there have been some cases where treatment with intravenous fluid alone was not successful and inotropic support was finally required (10). Cardiac dysfunction could have been the explanation for this observation. In 1998, Wali et al reported a significantly lower left ventricular ejection fraction in adult patients during the toxic stage of DHF compared to after recovery (4). Kabra et al and Khongphatthanayothon et al similarly reported a decreased ejection fraction in children with DHF during the toxic stage (2,3). No study has reported the cardiac function in patients with DF and no correlation between ejection fraction and the severity of the disease was found in the one study that looked into this issue (2).

While ejection fraction is widely used as an index of LV systolic performance, it is also well known as a load dependent index (3,11). The MPI is a new index of cardiac performance that combines systolic and diastolic function and is gaining widespread use in both adult and pediatric patients. The MPI is independent of geometry (12), is easy to perform and is reproducible. Although the effects of preload, afterload and heart rate to MPI (13,14) are still a mystery and need confirmation with further studies, MPI is now being widely used for the assessment of global ventricular function in...
Figure 2. (a) shows the myocardial performance index (MPI), and Figure 2. (b) shows the ejection fraction (EF), in patients with dengue virus infection during various stages of the disease (febrile, toxic, convalescent stages and follow up.)
Conv = convalescent stage; DF = dengue fever; DHF = dengue hemorrhagic fever; DSS = dengue shock syndrome; FU = follow up

Figure 2 (a)

Figure 2 (b)
clinical practice (15,16). The purpose of this study was to assess the cardiac function of patients with dengue virus infection with MPI and to assess the possible relationship between cardiac function and severity of clinical illness.

Our study confirmed the previous findings of cardiac dysfunction in DHF/DSS. Additionally, the degree of cardiac dysfunction measured by MPI also correlated with the clinical severity (grade) of the illness. The MPI during the toxic stage in patients with DHF was significantly higher than in patients with DF and the value was higher in cases with shock than in those cases with DHF without shock. The MPI improved toward normal during the convalescent stage. The EF during the toxic stage among the 3 groups showed a trend toward lower EF in patients with DHF and DSS than in patients with DF although this difference did not reach statistical significance. The reason(s) for lack of statistical significance when EF was used as the index of myocardial performance as opposed to the MPI is probably from the higher sensitivity or lower variability of the MPI as a measurement of cardiac performance. The MPI incorporates diastolic as well as systolic time interval in the measurement and thus could be more sensitive to diastolic dysfunction compared to EF. Diastolic function has been shown to be more sensitive to myocardial dysfunction associated with various cardiac diseases such as acute myocardial infarction(17) and transplanted heart rejection (18).

The cause(s) of cardiac dysfunction in DHF is still unknown. It may result from hypoperfusion, direct viral injury, or host responses to virus. Although many other viruses can trigger acute viral myocarditis, pathological studies of patients who died from DHF have not been supportive of this theory (19-21). Failure to detect elevated troponin T in any patients regardless of the severity in our study makes direct myocardial injury unlikely to be the cause of this cardiac dysfunction. The rapid time course of cardiac dysfunction in DHF and the mild to moderate degree of cardiac dysfunction (ejection fraction 53 9%) (3) make reversible functional impairment of myocardium due to ischemia or humoral factors more likely. Many cytokines are activated in patients with DHF as well as in bacterial sepsis (22-24). Some of these cytokines, especially the tumor necrosis factor-alpha (TNF-a) and interleukin-1b (IL-1b) have been shown to depress human myocardial function in vitro (25) and TNF-a has been found to be the myocardial depressant factor in patients with bacterial sepsis (26).

Regardless of the etiology, cardiac dysfunction in patients with DHF/DSS can have potential clinical implications. In patients with severe DHF and shock, it is unknown at this time if improving cardiac function with various medications that increase cardiac performance along with adequate fluid resuscitation would improve the clinical outcome. Since the main etiology of shock in DHF is depletion of the intravascular volume (26), it appears intuitive to begin with fluid resuscitation first and only reserve these medications for patients with refractory shock or documented cardiac dysfunction. Thus, in patients who do not respond to the usual regimen of fluid resuscitation, assessment of intravascular volume and cardiac function would be of tremendous value. Since invasive monitoring in patients with DHF is known to be notoriously difficult due to coagulopathy, echocardiograms could become the evaluation of choice due to their portability, non-invasiveness and ability to assess intravascular volume and cardiac function at the same time. The clinical usefulness of echocardiogram in the treatment of patients with dengue shock syndrome is another area awaiting evaluation in routine clinical practice.

In conclusion, this study confirms that the myocardial function in children with DHF/DSS using the myocardial performance index is impaired during the toxic stage compared with the convalescent stage and follow up. The degree of cardiac dysfunction correlates with the severity of the disease. There was no evidence of myocardial injury found in these patients. The cause(s) and significance of cardiac dysfunction in patients with dengue hemorrhagic fever and dengue shock syndrome are yet to be defined and deserve further study.

Acknowledgement

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References


Myocardial Performance Index (MPI) ใ ในผู้ป่วยดีแล้ว ไวรัสเหล่านี้ระยะต่างๆ

เพื่อศึกษาที่ศูนย์ขับไล่โรค, วิทยา, หลวงพ่อ, ศัลólogo, ยาคูน, โทษเหล่านี้ โรคทางที่มีภูมิทัศน์ที่นิลิ่น ภาควิชาการทางศาสตร์, คณะแพทยศาสตร์, จุฬาลงกรณ์มหาวิทยาลัย และ โรงพยาบาลจุฬาลงกรณ์, กรุงเทพฯ, ประเทศไทย

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาการทำงานของหัวใจของผู้ป่วยโดยใช้ Myocardial Performance Index (MPI)

วิธีการศึกษา: ตรวจค่า MPI ในผู้ป่วยระดับที่ติดเชื้อแล้ว ซึ่งได้รับการยืนยันทางภาควิชาการ ในระยะที่ 1, ระยะวิกฤติ, ระยะพัฒนา และหลังจากดับมิติ การรักษา เปรียบเทียบ MPI ระหว่างผู้ป่วยที่ติดเชื้อ (dengue fever, DF) ใช้ เลือดออกทีไม่เชื่อก (dengue hemorrhagic fever, DHF) และใช้เลือดออกที่ขอด (dengue shock syndrome, DSS) และราคาค่า troponin-T ในช่วงของผู้ป่วยจำนวน 10 คน (2 DSS, 6 DHF, 2DF)

ผลการศึกษา: ทำการศึกษาในผู้ป่วยจำนวน 49 คน (ชาย 29 คน, หญิง 20 คน) ซึ่งพบว่าค่า MPI ในผู้ป่วย DSS (0.44 ± 0.03) สูงกว่า DHF (0.41 ± 0.02) ซึ่งสูงกว่า DF (0.34 ± 0.02) อย่างมีนัยสำคัญ (p = 0.015) ค่า ejection fraction มีแนวโน้มต่ำกว่าในผู้ป่วย DSS (55.4 ± 7.0 %, DHF = 57.7 ± 8.6 %, DF = 60.9 ± 7.4 %, p = 0.077) ช่วง troponin-T อยู่ในเกณฑ์ปกติในผู้ป่วยทุกกลุ่มที่ตรวจ)

สรุป: การทำงานของหัวใจของผู้ป่วยค่าดีแล้วในผู้ป่วยได้เกือบออกในระยะวิกฤติ โดยความดีแล้วเพิ่มมากขึ้นในผู้ป่วยที่มีความรุนแรงของโรคมากขึ้น

คำสำคัญ: ใช้ยาคูน, ใช้ยาคูน ใช้ยาคูนที่ขอด, การทำงานของหัวใจ, myocardial performance index