Treatment of Severe Diphtheritic Myocarditis by Temporary Insertion of a Cardiac Pacemaker

Nguyen Minh Dung,1 Rachel Kneen,1,4 Nguyen Kiem,2 Delia B. Bethell,1,4 Nguyen Hoan Phu,7 Tom Solomon,1,4 Tran Thi Hong Chau,7 Nguyen Thi Hoang Mai,2 Nicholas P. J. Day,1,4 and Nicholas J. White1,4

1Wellcome Trust Clinical Research Unit, 2Centre for Tropical Diseases, Cho Quan Hospital, District 5, Ho Chi Minh City, Vietnam; and 4Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom

Vietnamese children and adolescents with diphtheritic myocarditis and severe conduction abnormalities were treated prospectively with temporary insertion of a cardiac pacemaker. Five of 32 patients died before the procedure could be performed; the remaining 27 patients underwent successful pacemaker insertion. In children and adolescents with diphtheritic myocarditis and severe conduction defects, temporary insertion of a cardiac pacemaker may improve the outcome.

Diphtheria is an important public health problem in much of the developing world and has had a recent resurgence in Eastern Europe and the former Soviet Union [1]. Diphtheria is also an important public health problem in southern Vietnam, where ~100 cases still occur every year (T. T. Hien, personal communication). Infection with toxigenic Corynebacterium diphtheriae may result in widespread toxin-mediated damage, particularly in the kidneys, nervous system, and heart (i.e., diphtheritic myocarditis) [2]. Diphtheritic myocarditis occurs in 10%–20% of patients who initially present with oropharyngitis. Overall, diphtheritic myocarditis has an associated mortality rate of ~60%, and it accounts for the majority of deaths related to diphtheria [3]. However, patients with myocarditis who survive appear to make a full recovery [4–6]. The principal manifestations of diphtheritic myocarditis are dilated cardiomyopathy and a variety of types of dysrhythmia and conduction disturbances. If complete heart block develops, the prognosis is almost always death [7, 8], and recovery has been reported in only a few cases [9, 10]. Whether temporary insertion of a cardiac pacemaker has a role in the treatment of diphtheritic myocarditis is uncertain [11], although this procedure appeared to have benefit for a patient who had second-degree heart block [12]. Therefore, we investigated Vietnamese children and adolescents who had severe diphtheritic myocarditis and bradyarrhythmias, and we looked for prognostic indicators to help identify which patients should be treated with temporary insertion of a cardiac pacemaker.

Patients and methods. This study was conducted at the Centre for Tropical Diseases, a referral center in Ho Chi Minh City for patients with diphtheria from southern Vietnam, and the Saigon Emergency Hospital (Ho Chi Minh City, Vietnam). The study was approved by the scientific and ethics committees of both health care centers, and written and oral informed consent was obtained from the parents of the patients. Because severe conduction defects associated with diphtheritic myocarditis are almost consistently fatal, we did not think that it would be ethical to randomize children and adolescents to not receive treatment with a temporary cardiac pacemaker once this option became available. Therefore, for the retrospective control group, we studied children and adolescents who had diphtheritic myocarditis with severe conduction defects and who presented to the Centre for Tropical Diseases in the 12 months before temporary insertion of a cardiac pacemaker was a treatment option.

From June 1992 through September 1995, we studied children and adolescents (age, <17 years) who had diphtheritic myocarditis and severe conduction disturbances and for whom temporary insertion of a cardiac pacemaker was indicated. Indications for temporary electrical cardiac pacing were severe bradyarrhythmias including either complete heart block, trifascicular block, or second-degree block with postural hypotension or syncope. For all patients, a characteristic adherent nasopharyngeal membrane must have been observed during the course of illness (either at the Centre for Tropical Diseases or at the referring local hospital). In addition, all patients had clinical evidence of severe myocarditis (with symptoms and signs of cardiac failure and enlargement) and had evidence of a severe conduction abnormality noted on an electrocardiogram. Patients with clinical evidence of diphtheritic myocarditis who did not develop a severe conduction abnormality were not included in the study but will be the subject of a separate report. A detailed medical history was obtained and a clinical exam-
mination was performed by a member of the study team. All details were recorded on standardized forms. Vital signs were recorded hourly or more frequently, as needed. For the control group, we examined the hospital charts of patients with diphtheritic myocarditis and a severe conduction defect (with an indication for temporary insertion of a cardiac pacemaker) who were admitted to the hospital in the 12 months before the cardiac pacemaker procedure was introduced.

At the time of enrollment in the study and as often as necessary, blood samples were obtained for determination of the hematocrit level, differential WBC count, and platelet count and for plasma biochemical analysis. Blood samples were obtained serially for measurement of cardiac enzyme and troponin T levels. We isolated C. diphtheriae from throat or nasal swabs on tellurite medium, and the findings were confirmed by means of standard biochemical tests (API Coryne; bioMérieux) [6]. Toxin production was demonstrated by use of the Elek immunodiffusion method [13].

At admission to the hospital, patients were treated with equine diphtheria antitoxin (40–100,000 IU im), when available, and benzylpenicillin (100,000 IU/kg iv q.d. for 14 days), in accordance with World Health Organization (WHO) guidelines [14]. Oxygen was administered via a facial mask. Patients with severe tonsillar and laryngeal edema were treated with hydrocortisone (2–4 mg/kg iv q.d. for 5–7 days). Tracheostomy was performed if edema or the laryngeal membrane caused airway obstruction. Pulmonary edema was treated with frusemide (1 mg/kg iv, as required). Cardiogenic shock was treated with inotropic infusions of dopamine (2.5–10 μg/kg/min iv) or dobutamine (2.5–10 μg/kg/min iv). No facilities existed for mechanical ventilation at the time of this study.

Twelve-lead electrocardiography was performed at the time of enrollment in the study, after pacemaker insertion, and either daily or as clinically indicated. Before September 1993, patients were transferred ~2.4 km to the Saigon Emergency Hospital for insertion of a pacemaker wire. Since September 1993, the procedure has been performed at the Centre for Tropical Diseases. A temporary pacemaker wire is inserted via the femoral, subclavian, or internal jugular vein by means of fluoroscopic guidance with use of a sterile technique, and the position was checked radiologically. Pacemakers were set to “demand” at a rate of 80–120 beats/min, with a voltage 3 times the threshold, and they were left in situ until the patient recovered or died.

When cardiac echocardiography became available at the Centre for Tropical Diseases, Doppler echocardiography (Sigma HCVD 44) was performed to estimate the ejection fraction from 2-dimensional images, and the cardiac index from the aortic root cross-sectional area and maximum blood viscosity and ejection time [15].

For comparisons of the 2 outcome groups, categorical data were analyzed using Fisher’s exact test. Nonparametrically distributed continuous variables were analyzed using the Mann-Whitney U test [16].

Results. Forty-eight children and adolescents with diphtheritic myocarditis and severe conduction disturbances were studied. Thirty-two of these patients were studied prospectively (30 had complete heart block, 1 had trifascicular block, and 1 had second-degree heart block with syncope), and 16 were studied retrospectively (15 had complete heart block and 1 had trifascicular block). In 38 patients, the nasopharyngeal membrane was still present; in 9 patients, the nasopharyngeal membrane had cleared and cardiac abnormalities were the only findings at the time of enrollment in the study. Echocardiography was performed for 9 patients, and the findings for all 9 patients were abnormal. Six of these 9 patients had dyskinesia of the intraventricular septum, 1 had a dilated left ventricle, 7 had a reduced ejection fraction, and 7 had a reduced cardiac index. The median ejection fraction was 42% (range, 25%–64%; normal, >55%), and the median cardiac index was 1.9 L/min/m² (range, 1.2–3.1 L/min/m²; normal, >2.8 L/min/m²). Persons who died did not differ significantly from those who lived with regard to these indices. For 4 patients (3 of whom died), it was possible to compare the cardiac index before and after pacemaker insertion, and the cardiac index was found to have increased by 110%–290%. The creatinine kinase level was elevated in all 12 patients in whom it was measured (median, 922 IU/L; range, 203–3934 IU/L); in these patients, the median creatine kinase–MB (cardiac fraction) mass level was 43.9 ng/mL (range, 22–96.9 ng/mL), and the median troponin T level was 3.4 ng/mL (range, 0–18.4 ng/mL). The median plasma creatinine level at the time of pacemaker insertion was 2.3 mg/dL (range, 1.6–4.6 mg/dL) in patients who died of diphtheritic myocarditis, and it was 1.0 mg/dL (range, 0.6–1.1 mg/dL) in those who survived (P = .013). One patient had hyperkalemia, but there were no differences between outcome groups with regard to electrolyte level or complete blood cell count.

Seven (26%) of the 27 patients who received a temporary cardiac pacemaker survived, compared with 0 of the 16 patients who did not receive a cardiac pacemaker (mean difference, 26%; 95% CI, 9%–42%; P = .03). Additional abnormalities noted on the electrocardiograms of the prospectively studied patients included frequent ventricular ectopic beats in 12 patients, a prolonged rate-corrected QT interval (range, 0.48–0.67 s) in 19, T-wave inversion in 14, and “ischemic” ST changes in 7. The median heart rate of all patients was 48 beats/min (range, 17–100 beats/min), and the median systolic blood pressure was 80 mm Hg (range, 60–100 mm Hg). Five of the prospectively studied patients who were in extremis, who had hypotension and severe bradycardia, developed ventricular fibrillation while preparations for pacemaker insertion were being made. Attempts to resuscitate these patients were unsuccessful. Twenty-seven patients had a pacemaker inserted, and their
heart rates restored. Seventeen patients (63%) died with the pacemaker in situ, 3 (11%) died after the pacemaker was removed, and 7 (26%) survived. The presenting clinical features of the patients who survived and those who died in the prospectively studied group are compared in table 1.

Patients with conduction disturbances before day 10 of illness were more likely to die than were other patients (21 [88%] of 24 patients vs. 4 [50%] of 8), for a sensitivity of 84% (95% CI, 71%–97%), specificity of 57% (95% CI, 40%–74%), a positive predictive value of 88%, and a negative predictive value of 50% (P = .046). Renal impairment was also associated with poor outcome (table 1), and all 10 patients with bleeding diathesis died, for a sensitivity of 40% (95% CI, 23%–57%), a specificity of 100%, a positive predictive value of 100%, and a negative predictive value of 30% (P = .05).

Despite restoration of a normal heart rate, 17 patients died with the pacemaker in situ. For these patients, the median time to death was 61 h (range, 16–211 h). Although blood pressure initially responded to the paced heart rate, and although the patients showed clinical improvement, progressive cardiac failure, with a gallop rhythm, hepatomegaly, pulmonary edema, and oliguria, was noted. The cardiac index continued to decrease, despite administration of inotropic support. Twelve patients developed ventricular tachycardia as an agonal event 2–6 h before death.

Ten patients had reversion to sinus rhythm and had the pacemaker removed. The median number of days that use of the pacemaker was required was 9.5 (range, 7–28 days). Three of these patients subsequently died: one developed progressive cardiac failure and right-side hemiplegia 2 days before death; one developed diphtheritic neuropathy and underwent ventilation by hand-bagging of the tracheostomy tube for respiratory paralysis on day 46, but died of cardiac failure 5 days later; and the other patient developed complete heart block again (2 days after the pacing wire was removed) and died before the pacemaker could be reinserted. Nineteen (95%) of the 20 patients who died after insertion of the pacemaker had hypotension that required treatment, compared with only 1 (14%) of the 7 patients who survived (mean difference, 81%; 95% CI, 53%–108%; P < .0001). Four of the 7 patients who survived developed diphtheritic neuropathy, including 1 patient who required ventilation by hand for 14 days; all had a full recovery.

Discussion. Diphtheria was once one of the most feared conditions to affect children and adolescents, causing death due to acute laryngeal obstruction, myocarditis, or respiratory paralysis. After mass immunization against diphtheria was introduced in the 1940s and 1950s, diphtheria was almost eradicated in Western countries, although it has continued to be an important cause of childhood death in the developing world. However, in the mid-1990s, there were large epidemics of diphtheria in Eastern Europe and the former Soviet Union. In 1995, there were an estimated 150,000 cases and 8000 deaths worldwide [17]. Although mass-vaccination programs and other infection-control mechanisms have improved the situation in the

### Table 1. Clinical characteristics of and laboratory findings for 32 children and adolescents with diphtheritic myocarditis for which temporary insertion of a cardiac pacemaker was required.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients who died (n = 25)</th>
<th>Patients who survived (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (range)</td>
<td>9.6 (5–16)</td>
<td>10.7 (5–13)</td>
</tr>
<tr>
<td>Corynebacterium diphtheriae isolated</td>
<td>13 (52)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Incomplete immunization</td>
<td>23 (92)</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Pacemaker required before day 10 of illness</td>
<td>21 (84)</td>
<td>3 (43)a</td>
</tr>
<tr>
<td>Antitoxin therapy administered</td>
<td>21 (84)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>“Bull neck”</td>
<td>19 (76)</td>
<td>4 (57)</td>
</tr>
<tr>
<td>Bleeding tendency</td>
<td>10 (40)</td>
<td>0 (0)b</td>
</tr>
<tr>
<td>Nasopharyngeal membrane present</td>
<td>18 (72)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Underwent tracheostomy</td>
<td>3 (12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Major abnormality noted on electrocardiogram</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete heart block</td>
<td>25 (100)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Trifascicular block</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Second-degree heart block with syncope</td>
<td>0 (0)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Creatinine level, median mg/dL (range)</td>
<td>2.3 (1.6–4.6)</td>
<td>1.0 (0.6–1.1)b</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless otherwise indicated.

a. P < .05.
b. P = .05.
newly independent states of the former Soviet Union, diphtheria remains a considerable global problem, and it caused an estimated 4000 deaths in 1999 [18].

The majority of the deaths result from toxin-mediated complications (e.g., myocarditis or respiratory failure secondary to peripheral neuropathy) [19]. In addition, early upper-airway obstruction due to laryngeal edema, renal failure, and disseminated intravascular coagulation contribute to the associated mortality. The case-fatality rate improved dramatically after the introduction of antitoxin therapy, tracheostomy, and intubation during the end of the 19th century; since then, it has remained constant at ~10% [2, 20].

Diphtheria toxin inhibits elongation factor-2 activity in protein synthesis and causes DNA fragmentation and cytolysis [21]. The myocardium shows hyaline degeneration and necrosis associated with active inflammation in the interstitial spaces. Conduction tissue is also affected [22]. Approximately 50% of patients with diphtheritic myocarditis develop severe conduction abnormalities, which usually are associated with fatal outcomes. In agreement with the findings of previous studies, at our center, the mortality rate for children and adolescents with diphtheritic myocarditis and complete heart block was 100% before the insertion of cardiac pacemakers was a treatment option [7, 8, 23].

In the present study, the introduction of temporary cardiac pacemakers was associated with a reduction in the mortality rate to 74%. Although general supportive care was improving at the time of the study, other than temporary pacemaker insertion, there were no clear differences between patients who died and those who survived to account for this improvement. This is the first report of successful use of temporary cardiac pacemakers for the treatment of patients with diphtheritic myocarditis and complete heart block. Temporary insertion of a pacemaker was successful for treatment of a South African child with second-degree atroventricular block [12], but it was unsuccessful for the treatment of 8 children (including 7 with complete heart block) in Chile [11]. Complete heart block is known to be a marker of severe myocardial damage [8], but this larger series identified a subgroup of patients with complete heart block for whom temporary use of a cardiac pacemaker was successful, presumably because of preferential damage to the conducting system with adequate pump function. In this study, 17 patients died with a pacemaker in situ. These patients became hypotensive despite the restoration of a normal heart rate, presumably because of continuing extensive toxin-mediated myocardial damage. Although antitoxin neutralizes circulating toxin, it has no effect on toxin that has already penetrated cells. The need for inotropic support after pacemaker insertion was a poor prognostic sign. Although the number of patients studied was small, cardiac enzymes indicated that there was more-severe myocardial damage in patients with fatal cases.

In such patients, emergency heart transplantation may be helpful, but this is unlikely to be an option in regions where diphtheria occurs.

Insertion of a pacemaker in children and adolescents who are severely ill with diphtheria is a difficult and potentially life-threatening procedure. The anatomical landmarks usually are obscured by severe neck edema and lymphadenopathy of “bull neck,” there is often a bleeding diathesis, patients may be hypoxic and confused, and there is risk of sudden respiratory arrest resulting from dislodgement of the membrane. In addition, the damaged myocardium may be irritable, and tachyarrhythmias may be provoked [5]. In most countries where diphtheria occurs, the facilities at which temporary pacemaker insertion can be performed are limited. In the present study, the rapid development of conduction disturbances (before day 10 of the illness), the presence of a bleeding diathesis, and the development of acute renal failure before insertion of the pacemaker were poor prognostic indicators. In countries where resources are limited, these clinical features may help identify patients who are most likely to benefit from use a pacemaker and ensure that those for whom there is no hope of survival are not subjected to this procedure.

In summary, >25% of children and adolescents survived after a cardiac pacemaker was temporarily inserted for the treatment of severe conduction disturbances in association with diphtheritic myocarditis. Complete heart block should no longer always be considered fatal in patients who have diphtheritic myocarditis—temporary insertion of a cardiac pacemaker may improve the outcome.

Acknowledgments

We thank the directors and staff of the Centre for Tropical Diseases, Cho Quan Hospital, and the Saigon Emergency Hospital—in particular, Tran Tinh Hien, Pham Ngoc Giao, and the doctors and nurses on the Malaria Research Ward; Nguyen Thi Tuyet Hoa, John Wain, and Christopher Parry, for microbiological assistance; Keith Channon, for cardiological advice; and Ann Taylor and Annie Siemieniuk, for performing biochemical investigations.

References

5. Bethell D, Dung N, Loan H, et al. Prognostic value of electrocardio-


