Does the risk of infective endarteritis justify routine patent ductus arteriosus closure?

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Objectives The risk of infective endarteritis in patients with patent ductus arteriosus seems to have declined during the last 30–40 years, and cases of patent ductus arteriosus complicated by infective endarteritis are now very rare. Moreover, with the introduction of antibiotics, there has been a dramatic reduction in mortality from infective endocarditis. Despite these changes, however, the prevention of infective endarteritis has remained the principal indication, apart from haemodynamic reasons, for surgical patent ductus arteriosus closure. The aim of this study was to ascertain whether prevention of infective endarteritis is still a justifiable indication for routine closure in all cases of patent ductus arteriosus.

Methods The records of 270 paediatric and adult cases of patent ductus arteriosus was reviewed with respect to infective endarteritis. All Swedish death certificates issued during the period 1960–93 were checked for the occurrence of patent ductus arteriosus in combination with infective endarteritis.

Results There had been no cases of infective endarteritis over an aggregate of 1196 years at risk. Of nearly three million deaths in Sweden during the period 1960–93 two cases were due to infective endarteritis as a complication of patent ductus arteriosus.

Conclusion The present findings suggest routine closure of a patent ductus arteriosus, for the sole purpose of eliminating the risk of infective endarteritis, is unnecessary.

Key Words: Patent ductus arteriosus, infective endarteritis.

Introduction

During the pre-antibiotic era, infective endarteritis was a fatal complication of patent ductus arteriosus and the most common cause of death (45%) in patients with patent ductus arteriosus. The annual risk of infective endarteritis in patients with patent ductus arteriosus at that time was estimated to be 0.45%. With the introduction of antibiotics and surgical closure of the ductus, there has been a manifest reduction in the number of cases of patent ductus arteriosus complicated by infective endarteritis, and the risk of death has been considerably reduced. Despite these changes, however, the prevention of infective endarteritis has remained a main and imperative indication for closure of patent ductus arteriosus.

The more sensitive diagnostic methods available today, in particular colour Doppler echocardiography, enable haemodynamically insignificant and even silent patent ductus arteriosus to be identified, that is cases where the sole reason for closure of the ductus would be to prevent infective endarteritis.

Material and methods

We reviewed, with respect to infective endarteritis, the records of all patients born since 1 January 1980 with patent ductus arteriosus diagnosed at the Department of Paediatric Cardiology in Lund, and of all adult patients who have come to our attention at the Department of Cardiology in Lund since 1989 and who were known to have or have had patent ductus arteriosus. Although the catchment area of our hospital has changed somewhat during recent years, it may be said to have represented a population of about 1.5–2 million (about one fifth of the national population) during the period 1980–95. Infants with surgical or spontaneous closure of the ductus within the first month of life, those with a co-existing very complicated cardiac malformation, and those with...
Table 1  The time at risk of infective endarteritis (IE), the incidence of infective endarteritis and clinical characteristics in the three different age groups

<table>
<thead>
<tr>
<th>Age at last verification of PDA</th>
<th>Total time at risk of IE, years</th>
<th>Cases with IE (n)</th>
<th>Other congenital heart disease %</th>
<th>Down's syndrome %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 months</td>
<td>54</td>
<td>0</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>1-10 years</td>
<td>456</td>
<td>0</td>
<td>29</td>
<td>8</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>686</td>
<td>0</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>1196</td>
<td>0</td>
<td>36</td>
<td>12</td>
</tr>
</tbody>
</table>

PDA = patent ductus arteriosus.

Table 2  Echocardiographic assessment of left ventricular and atrial size in the three different age groups

<table>
<thead>
<tr>
<th>Age at last verification of PDA</th>
<th>Normal/Enlarged/No result (n)</th>
<th>Normal/Enlarged/No result (n)</th>
<th>Enlargement of both left ventricle and atrium (n)</th>
<th>Normal size of both left ventricle and atrium (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-12 months</td>
<td>49/54/7</td>
<td>36/64/10</td>
<td>43</td>
<td>26</td>
</tr>
<tr>
<td>1-10 years</td>
<td>66/64/13</td>
<td>65/65/13</td>
<td>45</td>
<td>46</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>9/6/2</td>
<td>9/6/2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>124/124/22</td>
<td>110/135/25</td>
<td>93</td>
<td>80</td>
</tr>
</tbody>
</table>

PDA = patent ductus arteriosus

a ductus-dependent circulation were excluded from analysis. However, patients with concomitant ventricular or atrial septal defects, coarctation of the aorta, or pulmonary or aortic valve lesions were included as was one patient with hypertrophic cardiomyopathy.

Of the 281 patients who fulfilled the inclusion criteria, the records of 11 patients in the paediatric group could not be traced and they were therefore excluded from analysis. Of the remaining 270 patients, 178 (66%) were female and 92 (34%) male. Of the 173 patients (64%) with isolated patent ductus arteriosus, two had Eisenmenger syndrome, a 36-year-old woman and a 4-year-old girl with Down's syndrome.

The time at risk of infective endarteritis was defined as the age of the patient on the last occasion the ductus was demonstrably patent (i.e. at operation, Doppler echocardiography or angiography). According to the time at risk of infective endarteritis, the series was divided into three groups; infants (1-12 months), children (1-10 years), and those older than 10 years.

Infective endarteritis was defined as the presence of the clinical picture typically associated with positive blood cultures or echocardiographic vegetations, or findings consistent with infective endarteritis at postmortem examination. The haemodynamic consequence of the patent ductus arteriosus was determined by echocardiographic evaluation, haemodynamic significance of the ductus being considered negligible if both left ventricle and atrium were of normal size. Echocardiographic data were available in 92% (248/270) of cases.

The national bureau of statistics, Statistics Sweden (Statistiska Centralbyrån), checked all Swedish death certificates issued during the period 1960–93 for the occurrence of patent ductus arteriosus in combination with infective endarteritis. In Sweden, the diagnoses of death on the certificates are supplied by the treating physician who must be qualified or by the pathologist if a postmortem examination is undertaken. During the period 1969–90 autopsy frequency has declined in Sweden, from about 45% to barely 30%[6]. In the age group 0-44 years the reduction has been less, from approximately 70% to about 60% of all deaths. Since 1951 Swedish cause-of-death statistics have been collected, classified and edited according to the International Classification of Diseases (ICD) which contains specific terms for both patent ductus arteriosus and infective endocarditis.

Results

In the entire series (n: 270), representing an aggregate of 1196 years at risk of infective endarteritis, there was no case of this disease (Table 1). The 173 patients with isolated patent ductus arteriosus represented 994 years at risk.

Of 32 patients (11.8%) with Down's syndrome (Table 1), 15 had isolated patent ductus arteriosus, representing 8.7% of all cases of isolated patent ductus arteriosus. The echocardiographic data are given in Table 2. In 80 (30%) of the patients neither the left ventricle nor the left atrium was enlarged. Of the 173 patients with isolated patent ductus arteriosus, it was clinically silent in 38, diagnosis being made solely by Doppler echocardiography. Of these 38 patients, both the left ventricle and atrium were normal in size in 20 cases.
In 39 patients the decision was to leave the duct patent. Eleven of these 39 belonged to the group of 17 patients who had been at risk of infective endarteritis for more than 10 years. One of these 11 was a 36-year-old woman who had Eisenmenger syndrome. In the remaining 10 patients the left ventricle and atrium were normal in size, with the exception of two cases, one of whom was a 79-year-old asymptomatic woman with a normal-sized left ventricle but an enlarged left atrium.

According to official statistics, of 2,951,533 deaths in Sweden during the period 1960–93, in two cases, the death was attributable to patent ductus arteriosus complicated by infective endarteritis. In the first case, that of a 33-year-old woman who died in 1971, the postmortem examination also revealed the presence of 'cor pulmonale chronicum', which suggests that Eisenmenger syndrome was present. The second case was that of a 42-year-old woman who died in 1981, but no postmortem examination was performed. Both these cases occurred outside the catchment area of our hospital.

**Discussion**

Estimation of the risk of infective endarteritis in cases of patent ductus arteriosus is an important issue affecting clinical decisions. Since the advent of Doppler echocardiography, enabling clinically silent and haemodynamically insignificant patent ductus arteriosus to be detected, this issue has become even more pressing, and the need to re-estimate the incidence of infective endarteritis in patent ductus arteriosus is obvious. According to Houston and colleagues, the incidence of patent ductus arteriosus is probably higher than formerly thought, and this might be reflected in the present study where diagnosis was exclusively based on Doppler echocardiography in 38 of 173 patients with isolated patent ductus arteriosus. Compared with the general population, there was a very high proportion of patients with Down's syndrome both in our series as a whole, and in the isolated patent ductus arteriosus subgroup. This might represent a true difference not recognised before, but it might also reflect the practice of routine examination by Doppler echocardiography of all or nearly all patients with Down's syndrome because of the high incidence of other cardiac malformations occurring in conjunction with trisomy 21. To the best of our knowledge, no prospective study has been made of patent ductus arteriosus and infective endarteritis.

In the present series, with an aggregate of 1,196 years at risk, infective endarteritis was found not to have occurred. We consider the series to have been unbiased because our hospital in the southern part of Sweden is the only referral centre for congenital heart disease, and there is widespread agreement as to the necessity of surgical closure in cases of patent ductus arteriosus. Nonetheless, according to official statistics, there has been no case of fatal infective endarteritis associated with patent ductus arteriosus in our catchment area during the last 34 years.

Campbell estimated the annual risk of infective endarteritis as a complication of patent ductus arteriosus to be more than 0.45% [1]. Application of that risk level to the present series (n = 270) would yield about five expected cases of infective endarteritis. Schröder and Kadel, who retrospectively analysed 100 adult patients with patent ductus arteriosus who were referred for transcatheter closure [2], found six cases in whom infective endarteritis had been diagnosed, corresponding to an annual incidence of 0.14%. It is reasonable to suppose that one of the reasons for referral was the episode of infective endarteritis, resulting in an over-estimation of the general risk of infective endarteritis. Awadallah and colleagues reported 42 patients with congenital heart disease and infective endocarditis between 1970 and 1990, none of whom had patent ductus arteriosus [2]. During the period 1966–95, according to Medline, there were 13 reported cases of infective endarteritis complicating patent ductus arteriosus, in addition to the six cases reported by Schröder and Kadel.

Thus, it would appear that, at least in the industrialised world, infective endarteritis complicating patent ductus arteriosus is very rare nowadays and that the risk is very low. Surgical closure of the duct may of course explain the reduced number of patients with patent ductus arteriosus complicated by infective endarteritis, but hardly the decline in incidence among those still at risk (i.e. those who are not operated on). As only a minority of cases of infective endocarditis can be attributed to surgical and dental procedures [3, 4], the use of antibiotic prophylaxis is insufficient to explain the low incidence of infective endarteritis in patients with patent ductus arteriosus, especially since there are doubts about the efficacy of such prophylaxis [5]. In the present study, we were unaware to what extent the patients may have undergone antibiotic prophylaxis, but there was no reason to believe that it had been used before the diagnosis of patent ductus arteriosus was made. Changes in socio-economic circumstances, dental health and microbiological patterns may be factors, not investigated in this study, which might explain the decline in the risk of infective endarteritis.

Is the size of a patent ductus arteriosus a determinant of the risk of infective endarteritis? Owing to the absence of infective endarteritis in our clinical series, which included patients with both clinically silent, small and large ducts, the present findings provide no answer. However, it is likely that in the two fatal cases of infective endarteritis complicating patent ductus arteriosus since 1963, the patency was of haemodynamic significance. Owing to the much more sensitive diagnostic tools available today, in particular Doppler echocardiography, it is likely that the proportion of patients with a small patent ductus arteriosus was higher in our series than in that reported by Campbell [1], and that this might have contributed to the reduction in risk, assuming a small duct to be less susceptible than a large one to infective endarteritis. In the adult series studied by Schröder and Kadel, the luminal diameter of the patent ductus arteriosus was less than 4.5 mm in 60% of the
cases, but 4.5 mm or more in all six cases complicated by infective endarteritis\textsuperscript{[7]}. Latson and coworkers have shown animals with a trivial residual shunt after PDA umbrella implantation to be no more susceptible to infective endarteritis than controls, while the presence of a significant shunt, irrespective of the presence of a PDA umbrella, resulted in high susceptibility to infective endarteritis\textsuperscript{[9]}. These findings suggest small ducts to be less susceptible to infective endarteritis than large ones. However, the risk is still prevalent even in a small ductus, as illustrated by the case of infective endarteritis associated with a clinically silent patent ductus arteriosus reported by Balzer and colleagues\textsuperscript{[10]}.

As there were no cases of infective endarteritis in our series, we could elicit no figures for mortality. On the other hand, national statistics showed patent ductus arteriosus complicated with infective endarteritis to have caused only two deaths in Sweden during the last 34 years and no deaths since 1981. Several reports have indicated that the introduction of antibiotics has substantially improved survival in infective endocarditis, which in the pre-antibiotic era was generally fatal\textsuperscript{[3]-\textsuperscript{5}}. In the study of Schr\"{a}der and Kadel, all six patients who had had infective endarteritis survived it\textsuperscript{[5]}. In the group studied by Johnson and colleagues, there were two cases of patent ductus arteriosus and infective endarteritis during the period 1953-62 and both patients survived\textsuperscript{[3]}.

Thus, it seems that modern therapy has changed infective endarteritis from a fatal complication of patent ductus arteriosus to one which is curable in most cases. Owing to the present low risk of infective endarteritis in patients with patent ductus arteriosus and the efficacy of modern therapy in the event of this complication, there is no reason to close a patent ductus arteriosus for the sole purpose of preventing infective endarteritis. An exception to this would be in the case of a patient with patent ductus arteriosus who has incurred infective endarteritis. What then remains for closure are cases where the ductus is of haemodynamic significance. However, if a small ductus is not routinely closed, the patient should be monitored for the possible development of infective endarteritis.

### References