Effect of Prenatal Diagnosis on Outcomes in D-Transposition of the Great Arteries

Jodi M. Bartlett, RN, BSN*; David Wypij, PhD*‡§; David C. Bellinger, PhD, MSc#; Leonard A. Rappaport, MD§**; Linda J. Heffner, MD, PhD‡§§; Richard A. Jonas, MD¶¶; and Jane W. Newburger, MD, MPH*§

ABSTRACT. Background. By decreasing preoperative morbidity, prenatal diagnosis could improve neurodevelopmental outcomes in infants with critical congenital heart disease. We explored the impact of prenatal diagnosis on perinatal and perioperative variables and on outcomes at 1 year of age.

Methods. We analyzed a database of children enrolled in prospective studies on surgical support techniques from 1988 to 2000. Selection criteria included a diagnosis of D-transposition of the great arteries with intact ventricular septum or ventricular septal defect, no extracardiac congenital anomalies, birth weight >2.3 kg, and repair by arterial switch procedure.

Results. Of 346 patients at enrollment, 25 had a prenatal diagnosis, and 321 did not. Children with prenatal diagnosis, compared with those without, had a lower likelihood of birth by spontaneous labor, lower birth weights, lower Apgar 5 scores, a higher rate of preoperative endotracheal intubation, and surgery at a younger age. They tended to have a lower incidence of fetal distress during labor. At 1 year of age, 272 patients were tested with the Psychomotor Development Index and Mental Development Index of the Bayley Scales. Mean z scores were similar in those with and without prenatal diagnosis for both Psychomotor Development Index (−0.92 ± 0.93 vs −0.88 ± 1.05) and Mental Development Index (−0.29 ± 1.13 vs −0.41 ± 0.93).

Conclusions. Infants with D-transposition of the great arteries with and without prenatal diagnosis differed with respect to perinatal and perioperative variables, but their development at 1 year of age was similar. Future studies should include a greater number of children with prenatal diagnosis and a variety of congenital heart lesions. Pediatrics 2004;113:e335–e340. URL: http://www.pediatrics.org/cgi/content/full/113/4/e335; congenital heart disease, D-transposition of the great arteries, cardiac surgery, child development, prenatal diagnosis.

From the Departments of *Cardiology, †Neurology, **Medicine, and ||Cardiovascular Surgery and the ¶Clinical Research Program, Children’s Hospital Boston, Boston, Massachusetts; §§Department of Obstetrics and Gynecology, Brigham and Women’s Hospital, Boston, Massachusetts; Departments of ¶¶Pediatrics, #Neurology, §§Obstetrics and Gynecology, and ¶¶¶Surgery, Harvard Medical School, Boston, Massachusetts; and ¶¶¶¶Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts.

Received for publication May 9, 2003; accepted Dec 8, 2003.

Reprint requests to (J.W.N.) Department of Cardiology, Children’s Hospital Boston, 300 Longwood Ave, Boston, MA 02115. E-mail: jane.newburger@ tch.harvard.edu

PEDIATRICS (ISSN 0031-4005). Copyright © 2004 by the American Academy of Pediatrics.
the Children’s Hospital Boston Institutional Review Board and conducted in accordance with institutional guidelines.

**Prenatal and Delivery Data**

The presence or absence of a prenatal diagnosis of D-TGA and delivery details (including notation of fetal distress) were abstracted from the maternal obstetric record.

**Perioperative Data**

The methods of each trial have been described. In the perioperative period, study nurses recorded the perioperative course, intraoperative conduct, and daily data on events, medications, respiratory status, laboratory studies, fluid inputs and outputs, and blood-product requirements.

**Follow-up at 1 Year of Age**

The Bayley Scales of Infant Development were administered by 1 of 4 developmental psychologists when the children were ~1 year old. Two versions of the Bayley Scales were used during the time period of this study. The 1993 version includes revisions made to the original 1969 Bayley Scales to achieve an average score of 100 in a normal population sample. Of note, the mean population scores on the 1969 version of the Bayley Scales were ~10 points higher than on the 1993 version. The Bayley Scales yield 2 standardized scores, the Psychomotor Development Index (PDI) and the Mental Development Index (MDI), which assess important milestones of cognitive, fine motor, and gross motor development. Additional information collected at the 1-year assessment included height, weight, head circumference, neurologic examination, and family social class (Hollingshead Scale: A. Hollingshead, *Four-Factor Index of Social Status*, unpublished manual, 1975).

**Statistical Methods**

The primary outcomes in this study were the PDI and MDI scores of the Bayley Scales. To allow data from the 2 versions of the Bayley Scales to be combined, we calculated z scores (standard deviation [SD] units) and the percent of patients with scores ≥2 SD below the contemporary population means. Linear regression was used to assess the effects of prenatal diagnosis on continuous outcomes, and logistic regression was used to assess the effects of prenatal diagnosis on dichotomous outcomes. We adjusted for family social class (Hollingshead Scale) in all regression models. We used independent-samples t tests to compare the prenatal diagnosis groups with respect to continuous variables that were distributed normally, Wilcoxon rank sum tests for continuous variables that were not distributed normally, and Fisher’s exact tests for categorical variables. The Mantel-Haenszel $\chi^2$ test for trend was used to assess time trends in dichotomous outcomes. All P values are 2-tailed.

**RESULTS**

We enrolled a total of 346 children with D-TGA and IVS or VSD. Twenty-five children (7%) had a prenatal diagnosis, and 321 (93%) did not. To assess potential temporal trends during the 12-year study period, we analyzed the rates of prenatal diagnosis and other perioperative factors by year of surgery (Fig 1). The overall incidence of prenatal diagnoses of D-TGA increased over time ($P$ for trend over time $= .004$). In the group as a whole, the incidence of preoperative acidosis significantly decreased over time ($P = .001$), whereas the incidence of preoperative intubation significantly increased over time ($P < .001$).

Characteristics of infants with and without prenatal diagnosis are summarized in Table 1. Patients with a prenatal diagnosis, compared with those without, had a significantly higher incidence of induction or no labor onset and a significantly lower incidence of spontaneous birth ($P = .004$). None of the children with a prenatal diagnosis, compared with 13% of children without a prenatal diagnosis, experienced fetal distress during labor ($P = .06$). Fetal distress in labor was not uniformly associated with cesarean delivery in the group diagnosed postnatally, because only 7% of these pregnancies were delivered by unscheduled cesarean section.

At delivery, the infants diagnosed prenatally, compared with those without prenatal diagnosis, tended to have lower gestational age ($P = .08$) and had significantly lower mean birth weight ($P = .008$). Apgar scores at 1 minute did not differ between the 2 groups but at 5 minutes were significantly lower in those children with a prenatal diagnosis ($P = .01$). Patients with a prenatal diagnosis, compared with those without, were significantly more likely to have undergone endotracheal intubation in the preoperative period ($P = .02$). Infants with a prenatal diagno-

---

**Fig 1.** Temporal trends in prenatal diagnosis and preoperative characteristics.
sis underwent surgical repair ~5 days earlier than those without a prenatal diagnosis ($P < .001$). The 2 groups did not differ significantly in the incidence of preoperative sepsis, seizures, or balloon atrial septostomy. We compared children with and without prenatal diagnoses in terms of intraoperative and postoperative characteristics (Table 2). The 2 groups were similar with respect to intraoperative perfusion variables including duration of circulatory arrest, total bypass time, and total support time. Also, postoperative characteristics including days with endotracheal intubation, days in the intensive care unit, and total days in hospital were similar between the 2 groups.

Of the 346 children enrolled, 7 (2%), all in the postnatal-diagnosis group, died before the 1-year follow-up examination, and 339 (98%) were alive at the time of the 1-year follow-up. Families of 39 children were not invited to return for testing due to residence outside the United States (7), parental inability to speak English (8), and lack of funding for travel reimbursement (24). Of the remaining 300 families, 15 declined participation, 7 were lost to follow-up, and 2 cancelled their travel after the terrorist attacks of September 11, 2001. Four additional patients returned for 1-year follow-up evaluations but did not have developmental examinations due to the child’s inability to speak English (2), autism (1), and intercurrent illness at the time of the scheduled follow-up evaluation (1). The remaining 272 children (91%) underwent medical history assessment and in-person developmental evaluation at 1 year of age; of these, 18 (7%) had a prenatal diagnosis of D-TGA, and 254 (93%) did not.

At developmental evaluation at 1 year of age, the mean $z$ scores for the PDI and MDI of the Bayley Scales of Infant Development were similar in children with and without prenatal diagnosis in analyses adjusting for social class (Table 3). Those with a prenatal diagnosis, compared with those without, had fewer scores $\geq$ 2 SD below the contemporary mean on the PDI (6% vs 17%, respectively), but this difference did not reach statistical significance. A similar proportion of children in the 2 groups had

---

**TABLE 1.** Characteristics of Children With D-TGA According to Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prenatal Diagnosis $(n = 25)$</th>
<th>Postnatal Diagnosis $(n = 321)$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of labor, %</td>
<td></td>
<td></td>
<td>.004‡</td>
</tr>
<tr>
<td>Spontaneous labor</td>
<td>36</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Induced labor</td>
<td>44</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>No labor onset</td>
<td>20</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Type of delivery, %</td>
<td></td>
<td></td>
<td>.11‡</td>
</tr>
<tr>
<td>Vaginal</td>
<td>64</td>
<td>78*</td>
<td></td>
</tr>
<tr>
<td>Cesarean section (elective)</td>
<td>32</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cesarean section (emergency)</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Fetal distress, %</td>
<td>0</td>
<td>13</td>
<td>.06‡</td>
</tr>
<tr>
<td>Birth characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38.9 ± 1.8</td>
<td>39.5 ± 1.3</td>
<td>.08§</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>3320 ± 286</td>
<td>3901 ± 524</td>
<td>.008§</td>
</tr>
<tr>
<td>Apgar score, 1 min</td>
<td>7.6 ± 0.8</td>
<td>7.4 ± 1.5</td>
<td>.21§</td>
</tr>
<tr>
<td>Apgar score, 5 min</td>
<td>8.0 ± 0.6</td>
<td>8.3 ± 1.0</td>
<td>.01§</td>
</tr>
<tr>
<td>Associated diagnosis of ventricular septal defect, %</td>
<td>32</td>
<td>29</td>
<td>.82‡</td>
</tr>
</tbody>
</table>

Preoperative characteristics

| Age at surgery, days          | 4.0 ± 1.9                     | 8.8 ± 13.0                      | <.001§     |
| Acidosis, %                   | 16                            | 20                             | .80‡       |
| Intubation, %                 | 96                            | 77                             | .02‡       |
| Social class†                 | 50 ± 16                       | 42 ± 14                        | .02§       |

Values are mean ± SD or percentage.

* The $P$ value was calculated by using Fisher’s exact test.
† The $P$ value was calculated by using the Wilcoxon rank sum test.
‡ The $P$ value was calculated by using the independent-samples $t$ test.

**TABLE 2.** Perioperative Characteristics of Children With D-TGA According to Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prenatal Diagnosis $(n = 25)$</th>
<th>Postnatal Diagnosis $(n = 321)$</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of circulatory arrest, min</td>
<td>20 ± 16</td>
<td>27 ± 21</td>
<td>.12*</td>
</tr>
<tr>
<td>Total bypass time, min</td>
<td>119 ± 24</td>
<td>118 ± 36</td>
<td>.86*</td>
</tr>
<tr>
<td>Total support time, min</td>
<td>139 ± 19</td>
<td>145 ± 36</td>
<td>.19*</td>
</tr>
<tr>
<td>Postoperative characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubation, days</td>
<td>4.0 ± 2.8</td>
<td>3.9 ± 4.6</td>
<td>.43†</td>
</tr>
<tr>
<td>ICU stay, days</td>
<td>6.0 ± 3.4</td>
<td>6.1 ± 5.4</td>
<td>.84†</td>
</tr>
<tr>
<td>Time to discharge, days</td>
<td>11.3 ± 7.0</td>
<td>10.6 ± 7.1</td>
<td>.83†</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

* The $P$ value was calculated by using the independent-samples $t$ test.
† The $P$ value was calculated by using the Wilcoxon rank sum test.
MDI scores ≥2 SD below the contemporary mean. Children with a prenatal diagnosis had significantly higher social class than those without (P = .02) (Table 1).

Surgical support techniques evolved over the course of the 3 studies from which subjects were drawn. Therefore, we performed multivariable regressions including the prenatal diagnosis group together with all of the following variables: associated diagnosis of VSD, duration of total circulatory arrest, pH and hematocrit at onset of low-flow bypass or total circulatory arrest, study year, and social class. Adjustment for surgical variables did not affect our study inferences regarding the influence of prenatal diagnosis. Of note, lower PDI z scores were significantly associated with longer duration of total circulatory arrest (P = .03) and lower hematocrit (P = .02). Lower MDI z scores were significantly associated with lower social class (P = .001), higher pH (P = .01), and associated diagnosis of VSD (P = .03).

Children with a prenatal diagnosis did not differ significantly from those with postnatal diagnosis with respect to neurologic examination, somatic growth, or head circumference at 1 year of age.

**DISCUSSION**

As the mortality of infants with critical CHD has declined, the high prevalence of neurologic and developmental abnormalities in survivors has assumed increasing importance. The mechanisms of acquired neurologic injury in this population have changed over the past 2 decades, because prostaglandin therapy has allowed patients with duct-dependent lesions to survive until surgery can be performed and the techniques of surgical and transcatheter intervention have been refined. Despite these advances, delays in diagnosis and treatment can be associated with preoperative cerebral ischemia/reperfusion injury. Prior data suggest that the preoperative condition of neonates with critical CHD (including D-TGA) is better in those with a prenatal diagnosis. To our knowledge, however, no published studies have examined the impact of prenatal diagnosis on later development.

We found that children with D-TGA in whom the diagnosis was made in the prenatal period, compared with those with postnatal diagnosis, were significantly less likely to be born by spontaneous labor, had significantly lower birth weight, were significantly more likely to be intubated preoperatively, and went to surgery at a significantly younger age. They also had significantly lower 5-minute Apgar scores, perhaps reflecting the obstetrician’s knowledge of the diagnosis. However, there was no difference between groups in the incidence of acidosis. At 1 year of age, children with a prenatal diagnosis were slightly less likely to have PDI scores at least 2 SD below the contemporary population mean, although this difference did not achieve statistical significance, perhaps due to limited power. The prenatal- and postnatal-diagnosis groups were similar in the proportion with low MDI scores, as well as in mean MDI and PDI scores.

Inferences concerning the effect of prenatal diagnosis on developmental outcome may be complicated by the presence of many other risk factors for brain injury in children with CHD. We studied a patient population in which potential confounding factors were limited. Infants with D-TGA have a low incidence of coexisting anomalies, have infrequent significant hemodynamic problems after surgery, and undergo reparative surgery at a relatively uniform age. Previous studies have shown that children with D-TGA have higher rates of neurodevelopmental problems than would be expected in a normal population, including a lower intelligence quotient; difficulties with expressive language and visual-spatial and visual-motor skills; and a high incidence of otoromotor apraxia. Thus, our study population seemed to be an ideal one in which to study the influence of prenatal diagnosis on later development. The absence of an important difference between the prenatal diagnosis groups may reflect timely diagnosis and effective treatment of neonates without

**TABLE 3.** Follow-up At 1 Year of Age According to Prenatal Diagnosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prenatal Diagnosis (n = 18)</th>
<th>Postnatal Diagnosis (n = 254)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developmental z scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDI</td>
<td>−0.92 ± 0.93</td>
<td>−0.88 ± 1.05</td>
<td>.98*</td>
</tr>
<tr>
<td>MDI</td>
<td>−0.29 ± 1.13</td>
<td>−0.41 ± 0.93</td>
<td>.94*</td>
</tr>
<tr>
<td>Scores ≥2 SD below contemporary mean, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDI</td>
<td>6</td>
<td>17</td>
<td>.20†</td>
</tr>
<tr>
<td>MDI</td>
<td>6</td>
<td>6</td>
<td>.81†</td>
</tr>
<tr>
<td>Neurologic exam results</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any abnormality, %</td>
<td>31</td>
<td>39</td>
<td>.60‡</td>
</tr>
<tr>
<td>Microcephaly, %</td>
<td>6</td>
<td>5</td>
<td>.56‡</td>
</tr>
<tr>
<td>Growth percentiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>29 ± 31</td>
<td>46 ± 34</td>
<td>.08§</td>
</tr>
<tr>
<td>Weight</td>
<td>47 ± 31</td>
<td>50 ± 30</td>
<td>.08§</td>
</tr>
<tr>
<td>Head circumference</td>
<td>43 ± 21</td>
<td>42 ± 23</td>
<td>.85§</td>
</tr>
</tbody>
</table>

Values are mean ± SD or percentage. Only the 272 children who returned for evaluation at 1 year of age are included.

* The P value is based on linear regression, with adjustment for family social class.
† The P value is based on logistic regression, with adjustment for family social class.
‡ The P value was calculated by using Fisher’s exact test.
§ The P value was calculated by using the independent-samples t test.
prenatal diagnosis. In patients with D-TGA born in the prostaglandin era, the variance in developmental outcome contributed by events occurring between birth and corrective surgery seems to be smaller than that contributed by genetic or congenital, intraoperative, postoperative, or sociodemographic variables.

We found a tendency toward a greater incidence of fetal distress in the group diagnosed postnatally. To our knowledge, the diagnosis of D-TGA should not be associated with fetal distress. Furthermore, because the diagnostic criteria for fetal distress in labor are not standardized, we could not delineate the nature of the difference between groups in its incidence, nor could we compare the incidence of fetal distress in our cohort to that in the general population. Recent data suggest a population-based incidence of cesarean delivery for nonreassuring fetal status in labor of 2% to 4%. 1,6

Patients in the group diagnosed prenatally had higher rates of induction and younger gestational age at delivery than those in the group diagnosed postnatally. We did not prospectively record the reasons for timing of delivery in individual subjects. We speculate that prenatal diagnosis virtually always results in referral for delivery to a tertiary center. To ensure that delivery takes place under controlled conditions with pediatricians and pediatric cardiologists available, it is common obstetric practice to induce labor after 38 to 39 weeks. Conversely, undiagnosed cases are typically managed in the community, where spontaneous labor is more likely. Children with prenatal diagnosis underwent reparative surgery significantly sooner after birth than those with postnatal diagnosis, almost certainly because they arrived in our intensive care unit at a younger age and hence were placed on the surgical schedule earlier. Finally, we speculate that the higher rate of preoperative intubation among infants with prenatal diagnosis could relate to specific practices at the tertiary care facilities at which these children were delivered.

This study should be interpreted in light of several limitations. The relatively small number of patients in the prenatal diagnosis group at 1 year of age limited our statistical power to exclude modest differences in development. It is possible that aspects of obstetric management associated with prenatal diagnosis had an adverse effect on developmental outcome that balanced its benefits. For example, lower birth weight among infants with prenatal diagnosis could reflect earlier induction of labor; in previous studies of term infants undergoing reparative open-heart surgery, lower birth weight was shown to predict lower scores on the Bayley Scales at 1 year of age. 6 The small number of patients in the prenatal diagnosis group limited our ability to perform multivariate analyses to explore this hypothesis. Aspects of intraoperative and perioperative intensive care management at the single center from which the study sample was drawn may differ from those at some other centers. Finally, our findings in this cohort of children with a single lesion may not be generalizable to children with other forms of critical CHD.

Although we did not find a significant relationship between prenatal diagnosis and development at 1 year of age, our data suggest several important temporal trends. We found that the proportion of D-TGA patients in whom diagnosis was made prenatally increased over time. Furthermore, the incidence of preoperative intubation in all patients (ie, those with and without a prenatal diagnosis) has increased over time, and the incidence of preoperative acidosis in all patients has decreased. Verheijen et al 15 reported that prenatal diagnosis of CHD decreased the likelihood of deterioration of acid-base equilibrium, but the incidence of preoperative acidosis was similar in our cohort among those with and without prenatal diagnosis.

CONCLUSIONS

Our data suggest that, among patients with D-TGA with IVS or VSD, prenatal diagnosis is associated with differences in perinatal and perioperative variables but does not improve development at 1 year of age. Additional follow-up is necessary to determine whether prenatal diagnosis affects later cognitive function as children approach school age. Future studies should include a greater number of children with a prenatal diagnosis as well as children with congenital heart lesions other than D-TGA.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health grants R01 HL41786 and RR 02172.

We are indebted to Ludmila Kyn for database and statistical programming; Kristin C. Lucius Thomas, RN, MS, and Amy Z. Walsh, RN, BSN, for data collection assistance; Kathleen M. Alexander for project coordination; and Donna M. Duva and Donna M. Donath for scheduling evaluations, arranging patient travel, and providing data-management assistance.

REFERENCES


2. Kumar RK, Newburger JW, Gauvreau K, Kamenir SA, Hornberger LK. Comparison of outcome when hypoplastic left heart syndrome and transposition of the great arteries are diagnosed prenatally versus when diagnosis of these two conditions is made only postnatally. Am J Cardiol. 1999;83:1649–1653


9. Bellingher DC, Wypij D, Kuban KCK, et al. Developmental and neurologic status of children at 4 years of age after heart surgery with...
hypothermic circulatory arrest or low-flow cardiopulmonary bypass. *Circulation.* 1999;100:526–532


Effect of Prenatal Diagnosis on Outcomes in D-Transposition of the Great Arteries

Pediatrics 2004;113:e335
DOI: 10.1542/peds.113.4.e335

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/113/4/e335

References
This article cites 14 articles, 5 of which you can access for free at:
http://pediatrics.aappublications.org/content/113/4/e335.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Fetus/Newborn Infant
http://classic.pediatrics.aappublications.org/cgi/collection/fetus:newborn_infant_sub
Cardiology
http://classic.pediatrics.aappublications.org/cgi/collection/cardiology_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since . Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2004 by the American Academy of Pediatrics. All rights reserved. Print ISSN: .

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™
Effect of Prenatal Diagnosis on Outcomes in D-Transposition of the Great Arteries
Pediatrics 2004;113:e335
DOI: 10.1542/peds.113.4.e335

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/113/4/e335