Amiodarone-Associated Thyroid Dysfunction
Risk Factors in Adults With Congenital Heart Disease

Sara A. Thorne, MD, MRCP; Isobel Barnes, MSc; Paul Cullinan, MD; Jane Somerville, MD, FRCP, FESC

Background—Amiodarone is widely used in adults with congenital heart disease, but no systematic study has been published on its effects on thyroid function in these patients. A retrospective study was performed to examine the frequency of amiodarone-associated thyroid dysfunction in adults with congenital heart disease and to identify any contributing factors.

Methods and Results—All adults (16 to 60 years old) with congenital heart disease were identified from a database if they had no preexisting thyroid disease, had taken amiodarone for ≥6 months, and were currently followed up by 1 consultant (J.S.). Ninety-two patients were found and evaluated for thyroid status and cardiac complications. A case-control analysis was performed, with patients matched for duration of amiodarone therapy. Of the 92 patients (age, 34.9±10.2 years; range, 18 to 60 years), 36% developed thyroid dysfunction: 19 became hyperthyroid and 14 hypothyroid. Female sex and complex cyanotic heart disease were significant risk factors for developing thyroid dysfunction (odds ratios, 3.0 and 7.00; \( P \leq 0.04 \) and 0.01, respectively). Previous Fontan-type surgery also appeared to be a risk factor for developing thyrotoxicosis (odds ratio, 4.0; \( P = 0.17 \)), and amiodarone >200 mg/d a risk factor for thyroid dysfunction (odds ratio, 4.0; \( P = 0.60 \)).

Conclusions—Amiodarone-associated thyroid dysfunction is common in adults with congenital heart disease. Women and those with complex cyanotic lesions are at particular risk, as patients may be who have had Fontan-type surgery or are taking >200 mg/d of amiodarone. Amiodarone should be used only when other antiarrhythmics are ineffective or contraindicated. Vigilance is required to detect and treat thyroid dysfunction.

Key Words: heart defects, congenital ■ amiodarone ■ thyroid

Amiodarone is used in adults with congenital heart disease, many of whom have a combination of poorly tolerated arrhythmias refractory to treatment with other antiarrhythmics and ventricular dysfunction that precludes the use of more negatively ionotropic alternatives. Thyroid dysfunction is a potentially serious complication of amiodarone therapy, with a prevalence of 1% to 24% in older patients with acquired heart disease (mean age, 50 to 66 years).\(^1\)\(^-\)\(^3\) However, there is no published systematic study on amiodarone-associated thyroid dysfunction in patients with congenital heart disease, who constitute a large population (>4000) in the Grown-Up Congenital Heart Disease Unit established in this institution. After 6 new cases of amiodarone-associated thyrotoxicosis were diagnosed in young women presenting with worsening arrhythmias and heart failure, it was decided to perform a retrospective survey of all adults with congenital heart disease on long-term amiodarone therapy. A case-control analysis was used to examine factors important in the development of thyroid dysfunction.

Methods

Study Population
All (92) living patients 16 to 60 years old with congenital heart disease who had taken amiodarone for ≥6 months and who remained under the current follow-up of 1 consultant (J.S.) were identified from a population of >4000 patients seen and registered on the Grown-Up Congenital Heart Disease Database. The database is a computerized record of all patients with congenital heart disease seen by J.S. over 20 years. All information was entered by a single database manager under the supervision of J.S. Patients were excluded from the study if they had any thyroid disease before the use of amiodarone or if they had not been seen within the year of the study. Patients were evaluated retrospectively from case records and prospectively in the clinic for clinical and laboratory evidence of thyroid and liver dysfunction and for cardiac status and complications. Ninety-two patients were studied, 46 men and 46 women, and the mean age was 34.9±10.2 years (range, 18 to 60 years).

The study population of 92 patients had a range of congenital cardiac lesions or types of surgical repair (Table 1), including repair of tetralogy of Fallot, Fontan-type surgery, aortic valve disease, repaired atrioventricular and atrial septal defects, Mustard repair of transposition of the great arteries, and congenitally corrected transposition. Patients with complex congenital heart disease included cyanotic patients who had either not been operated on or were
palliated and those who were not cyanotic who had undergone biventricular repair.

**Amiodarone Regimen**

The indication for amiodarone therapy was either failure to respond to other antiarrhythmics or contraindication to the use of negatively inotropic antiarrhythmics in the management of paroxysmal atrial fibrillation or flutter in 67 patients, ventricular tachycardia in 15, and reentry supraventricular tachycardia in 4 (Table 2). Amiodarone therapy was instituted according to the clinical situation, with either intravenous loading (1.2 g over 24 hours) or oral loading (600 mg/d for 1 week, followed by 400 mg/d for 1 week). The median maintenance dose was 200 mg/d, and the mean dose was $194 \pm 36$ mg/d (range, 100 to 300 mg/d). For the whole study population of 92 patients, the mean age at starting amiodarone therapy was $31.1 \pm 10.6$ years (range, 12 to 59 years), and the median duration of amiodarone therapy was 3 years (range, 0.5 to 15 years).

**Laboratory Measurements**

Laboratory criteria for diagnosis of hyperthyroidism were a suppressed plasma thyroid-stimulating hormone (TSH) in combination with an elevated serum thyroxine. Elevated thyroxine alone was not considered diagnostic of hyperthyroidism. Hypothyroidism was diagnosed if TSH was elevated and thyroxine reduced. Triiodothyronine and thyroglobulin were not routinely measured in our laboratory. Thyroid and liver function tests were performed by routine analysis with a Beckman CX7 Synchron.

**Case-Control Analysis and Statistical Methods**

Descriptive statistical analyses were carried out on the study population of 92 patients. A case-control analysis was performed; cases were defined as those patients who developed thyroid dysfunction while taking amiodarone, and controls as those who remained euthyroid. Each case was matched to a control on the basis of duration of amiodarone therapy, the controls having had to have taken amiodarone for at least 1 year longer than their matched cases. The following possible risk factors were explored: sex and cardiac diagnostic group or type of repair were analyzed as binary measures, dose was coded as a categorical variable with levels low ($<200$ mg/d amiodarone), medium (200 mg/d), and high ($>200$ mg/d), and age and measures of liver function were analyzed as continuous variables. Subset analyses were performed on hyperthyroid and hypothyroid patients, exploring the above potential risk factors. Analyses were carried out by conditional logistic regression analysis using the statistical package EGRET. Unless otherwise stated, descriptive data are expressed as mean±SD. Log-likelihood $\chi^2$ tests were used to determine statistical significance, which was inferred at $P<0.05$. 

**TABLE 1. Cardiac Diagnoses in the 3 Groups of Patients Taking Amiodarone**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Total Study Population (n=92)</th>
<th>Euthyroid (n=59), %</th>
<th>Hyperthyroid (n=19), %</th>
<th>Hypothyroid (n=14), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fontan-type repair</td>
<td>17</td>
<td>6 (35)</td>
<td>7 (41)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>Cyanotic CHD, unoperated or palliated</td>
<td>17</td>
<td>8 (47)</td>
<td>5 (29)</td>
<td>4 (24)</td>
</tr>
<tr>
<td>ASD/AVSD/MVD</td>
<td>15</td>
<td>12 (80)</td>
<td>3 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Fallot postradical repair</td>
<td>15</td>
<td>13 (87)</td>
<td>0</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Complex CHD, biventricular repair</td>
<td>9</td>
<td>6 (67)</td>
<td>2 (22)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Bicuspid aortic valve±coarctation, supra- and sub-AS</td>
<td>6</td>
<td>5 (83)</td>
<td>1 (17)</td>
<td>0</td>
</tr>
<tr>
<td>TGA Mustard</td>
<td>3</td>
<td>2 (67)</td>
<td>0</td>
<td>1 (33)</td>
</tr>
<tr>
<td>cTGA</td>
<td>3</td>
<td>3 (100)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other (familial or anomalous coronary-related cardiomyopathy, Noonan, Ebstein anomaly)</td>
<td>7</td>
<td>4 (57)</td>
<td>0</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

CHD indicates congenital heart disease; ASD, atrial septal defect; AVSD, atroventricular septal defect; MVD, mitral valve disease; AS, aortic stenosis; TGA, transposition of the great arteries; and cTGA, corrected TGA.

**TABLE 2. Indications for Amiodarone Therapy in the Whole Study Population**

<table>
<thead>
<tr>
<th>Diagnostic Group</th>
<th>Total Study Population (n=92)</th>
<th>Paroxysmal Atrial Flutter or Fibrillation (n=67)</th>
<th>Ventricular Tachycardia (n=15)</th>
<th>Ventricular Tachycardia and Paroxysmal Atrial Flutter or Fibrillation (n=6)</th>
<th>Reentry Tachycardia (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fontan-type repair</td>
<td>17</td>
<td>16</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Cyanotic CHD, unoperated or palliated</td>
<td>17</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ASD/AVSD/MVD</td>
<td>15</td>
<td>11</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Fallot postradical repair</td>
<td>15</td>
<td>8</td>
<td>3</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
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<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Bicuspid aortic valve±coarctation, supra- and sub-AS</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TGA Mustard</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>cTGA</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Other (familial or anomalous coronary-related cardiomyopathy, Noonan, Ebstein anomaly)</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
Thirty-one cases were matched with 1 control each. Controls could not be found for 2 cases, 1 hyperthyroid and 1 hypothyroid, who had taken amiodarone for 11 and 13 years, respectively. Statistical analysis was therefore performed on a total of 62 patients: 31 controls matched with 31 cases, 18 with thyrotoxicosis and 13 with hypothyroidism (Table 4).

Female sex and unoperated or palliated cyanotic heart disease were found to be significant risk factors for amiodarone-associated thyroid dysfunction (odds ratio, 3.00; \( P=0.31 \)) and other diagnostic groups with sufficient numbers for statistical analysis (previous Fontan-type surgery, repaired tetralogy of Fallot, and repaired atrial septal defect/atrioventricular septal defect) were not at increased risk of thyroid dysfunction when hypothyroidism and hyperthyroidism were considered together. Thyroid dysfunction appeared to follow a dose-dependent effect of amiodarone, the odds ratio for developing thyroid dysfunction being 2.00 for 200 mg/d and 4.00 for \( >200 \) mg/d amiodarone, but this effect was not statistically significant (\( P=0.6 \)). Age was not related to the development of thyroid dysfunction. Liver function tests had not been performed systematically, but in the 53% in whom they had been done, no significant relationship was found between derangement of liver function and thyroid dysfunction (all \( P>0.4 \), data not shown). After bivariate analysis, sex was not found to be a confounding factor.

**Subset Case-Control Analysis**

Previous Fontan-type surgery appeared to be a risk factor for thyrotoxicosis (odds ratio, 5.00), although this did not reach statistical significance (\( P=0.17 \)). Female sex and cyanosis also appeared to be risk factors for thyrotoxicosis (odds ratios, 3.00 and 4.00) but were no longer significant (\( P=0.08 \) and 0.17). Other cardiac diagnoses, age, dose, and liver function tests were not significantly associated with thyrotoxicosis (Table 4).

When data were analyzed to examine the relationship between cyanosis and hypothyroidism, there was nonconvergence, because none of the controls had hypothyroidism. This implies that cyanosis and amiodarone-associated hypothyroidism may be strongly related. Female sex appeared to be associated with hypothyroidism, but the effect was not significant (odds ratio, 3.00; \( P=0.31 \)). No other risk factors (other cardiac diagnoses, age, dose, and liver function tests) were identified for hypothyroidism.

Only 1 patient, a 28-year-old woman with repaired tetralogy of Fallot who had taken amiodarone for 4 years, became transiently thyrotoxic before starting myxedema. She had been biochemically euthyroid before developing myxedema. She had been positive antithyroid antibodies (anti-thyroglobulin, 1:100; anti-thyroid microsomal, 1:6400), and a diagnosis of Hashimoto’s disease was made. No patient who initially had amiodarone-associated myxedema subsequently developed thyrotoxicosis.

**Discussion**

There is a high prevalence of amiodarone-associated thyroid dysfunction in this population of adults with congenital heart disease. Female sex and cyanotic heart disease are significant independent risk factors for the development of thyroid dysfunction, a finding not previously described. Survivors of Fontan-type surgery may also be at particular risk of hyperthyroidism. Thyrotoxicosis is a particularly serious side effect of amiodarone in patients with congenital heart disease, and although this may be partly due to the notoriety of amiodarone in producing disarringly subtle clinical manifestations of thyrotoxicosis, in this study, >50% of hyperthyroid

**TABLE 3. Details of Amiodarone Therapy in the Whole Study Population**

<table>
<thead>
<tr>
<th>Sex, n (%)</th>
<th>Euthyroid (n=59)</th>
<th>Hyperthyroid (n=19)</th>
<th>Hypothyroid (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>25 (42)F</td>
<td>11 (58)F</td>
<td>10 (71)F</td>
</tr>
<tr>
<td>Female</td>
<td>34 (58)M</td>
<td>8 (42)M</td>
<td>4 (29)M</td>
</tr>
<tr>
<td>Age amiodarone started, y (range)</td>
<td>31.8±10.0 (17–58)</td>
<td>30.1±11.5 (12–56)</td>
<td>29.6±12.2 (16–57)</td>
</tr>
<tr>
<td>Age at thyroid dysfunction diagnosis (current age for euthyroid group, range), y</td>
<td>35.4±9.3 (18–59)</td>
<td>34.1±12.1 (20–59)</td>
<td>34.0±11.2 (20–60)</td>
</tr>
<tr>
<td>Duration of therapy, y, median (range)</td>
<td>3.0 (0.5–15)</td>
<td>2.5 (0.7–12)</td>
<td>3.5 (2–14)</td>
</tr>
<tr>
<td>Amiodarone dose, mg/d</td>
<td>191±28</td>
<td>201±39</td>
<td>200±60</td>
</tr>
</tbody>
</table>
patients presented with classic signs of thyrotoxicosis, with 20% requiring hospital admission. The combination of pre-existing impaired ventricular function, worsened tachyarrhythmias, and a high-output thyrotoxic state precipitated heart failure in these patients, who were additionally debilitated by weight loss, proximal myopathy, and agitation.

Action of Amiodarone on the Thyroid Gland
The high iodine content of amiodarone affects the peripheral metabolism of thyroxine. This may cause changes in thyroid function tests that are without clinical significance, particularly in the early months of therapy.3 The data in this study are not affected by such results, because we excluded patients who had taken amiodarone for <6 months and used strict diagnostic criteria for the biochemical diagnosis of thyroid dysfunction.3

The effects of amiodarone on the thyroid gland are likely to be mediated by its high iodine content, a daily maintenance dose of amiodarone of 200 mg representing a >10-fold increase in daily intake. However, how it causes thyrotoxicosis in some patients, myxedema in some, and yet has no effect in other patients is not understood. It has been suggested that amiodarone-induced myxedema predominates in areas in which the soil is iodide-replete and that thyrotoxicosis occurs in areas of iodide deficiency,4 although not all studies support this hypothesis.5,6 The widespread use of iodinated salt in foods in the UK makes it unlikely that patients in this study were iodine deficient. Iodine alters thyroid autoregulation and may induce thyroid hormone synthesis3 as well as precipitating Graves disease,7 and amiodarone has a direct cytotoxic effect on thyroid follicles3; all of these may contribute to the development of thyrotoxicosis.

Prevalence of Thyroid Dysfunction and Duration of Amiodarone Therapy
Although this study may have overestimated the frequency of amiodarone-associated thyroid dysfunction because of the select nature of the study population, it is higher than has been found in both retrospective and prospective studies of older patients with acquired heart disease,1–3,8 despite a lower
maintenance dose of amiodarone. Of interest, amiodarone appears to induce thyroid dysfunction in children only rarely, perhaps reflecting the low incidence of primary thyroid disease in children.

The case-control analysis did not examine duration of amiodarone therapy as a risk factor for thyroid dysfunction, but there appeared to be no difference in median duration of therapy between those who developed thyroid dysfunction and those who remained euthyroid. Our patients had taken amiodarone for longer than those in other studies, so it is not possible to exclude an effect of prolonged duration of therapy on thyroid dysfunction. We found that both myxedema and thyrotoxicosis developed at any time during amiodarone therapy, in contrast to other studies suggesting that amiodarone-associated hypothyroidism occurs rarely after the first 18 months of therapy.

**Risk Factors for Thyroid Dysfunction: Sex**

Previous studies have not identified female sex as an independent risk factor for amiodarone-associated thyroid dysfunction, perhaps because few young women were involved. Male patients predominated in other studies, and the mean ages of the study populations were 54 to 66 years, compared with 34.9 years in the present study. Although age was not demonstrated to be a risk factor for thyroid dysfunction within this study, it is possible that the relative youth of our patients does confer a risk greater than that found in studies of patients >60 years old.

The increased risk of amiodarone-associated thyroid dysfunction in women may be a reflection of their greater propensity to primary thyroid disease, such as Graves and Hashimoto’s disease. Graves disease occurs in ~2% of women and only ~0.2% of men, the incidence peaking at 20 to 40 years of age, similar both to the peak of 30 to 50 years for Hashimoto’s disease and to the mean age of our study population. Although all patients in this study were biochemically euthyroid when starting amiodarone, thyroid autoantibodies were not measured routinely, so it is possible that amiodarone precipitated the onset of preexisting autoimmune disease in some of our patients. Nonetheless, although preexisting anti-thyroid peroxidase autoantibodies and a family history of thyroid disease may increase the risk of amiodarone-associated myxedema, there is no evidence to date that underlying autoimmune disease influences the development of amiodarone-associated thyrotoxicosis.

**Risk Factors for Thyroid Dysfunction: Amiodarone Regimen**

There was a trend toward a dose-dependent response between amiodarone and thyroid dysfunction, confirming earlier work. In this study, the dose response was not statistically significant, probably because of the low dose and small dose range of amiodarone used in our study. The majority of patients in this study were taking amiodarone 200 mg/d, widely accepted as a low-dose regimen. Whether further reducing the dose of amiodarone would decrease the risk of thyroid dysfunction while maintaining antiarrhythmic efficacy requires further study.

**Risk Factors for Thyroid Dysfunction: Cardiac Diagnosis**

Unoperated or palliated complex cyanotic heart disease was a significant risk factor for the development of both hyperthyroidism and hypothyroidism, and survivors of Fontan surgery also appeared to be at particular risk of thyrotoxicosis. The latter did not reach statistical significance, perhaps because of insufficient power due to small numbers. Paroxysmal atrial tachycardias, predominantly atrial flutter, are common in Fontan survivors and are poorly tolerated and frequently difficult to control with antiarrhythmics other than amiodarone, which is thus widely used. Why cyanotic patients and those with previous Fontan-type surgery should be at particular risk of amiodarone-associated thyroid dysfunction is not clear.

It is possible that the elevated systemic venous pressure that results from Fontan-type surgery may alter the hepatic metabolism of amiodarone, increasing the iodine load it produces and therefore its effects on the thyroid gland. Liver function tests were not performed systematically in this study, but abnormalities in the data available were not significant risk factors for thyroid dysfunction. We did not measure plasma levels of amiodarone or its metabolites, so we cannot exclude the possibility that plasma amiodarone or desethyl amiodarone concentrations were higher in the cyanotic and Fontan patients than in other patients.

**Alternative Treatment Strategies**

Alternative therapies that avoid the long-term use of amiodarone are needed. Abnormal hemodynamics contributing to arrhythmia should be corrected, for example, pulmonary incompetence after repair of tetralogy of Fallot. Transcatheter radiofrequency ablation of atrial flutter has become a useful tool, but the technique is in its infancy for patients with complex atrial anatomy and previous atrial surgery, as is the case after Fontan or Mustard surgery. Early reports of Fontan conversion to total cavopulmonary connection with simultaneous ablative surgery and atrial reduction have had some success in reducing arrhythmia in children, but long-term recurrence rates are not yet known. Right ventricular tachycardia may be successfully ablated in patients with operated congenital heart disease; radiofrequency ablation for atrial fibrillation is a developing area that may be of use in the future.

**Further Studies**

Further prospective studies are needed to examine the mechanism of amiodarone-associated thyroid dysfunction and to further elucidate why adults with congenital heart disease, particularly women; cyanotic patients; and Fontan survivors are at high risk of this serious side effect. In addition to routine (serum thyroxine and TSH) thyroid and liver function testing, thyroid autoantibodies and both free and reverse triiodothyronine should be measured before amiodarone therapy is begun, and these as well as amiodarone levels should be monitored at regular, 6-month intervals thereafter.

**Conclusions**

This first investigation of amiodarone-associated thyroid dysfunction in adults with congenital heart disease shows that
it is a frequent complication that may appear after many years of therapy. Women and cyanotic patients are at increased risk of hyperthyroidism and hypothyroidism. Fontan survivors may have an increased risk of thyrotoxicosis. As a result of these findings, it is now our practice to avoid using amiodarone as a first-line antiarrhythmic. However, it is often the very patients who are the most likely to need amiodarone who are the least able to tolerate thyrotoxicosis, because of ventricular dysfunction and hemodynamically important arrhythmias unresponsive to other therapy. When use of amiodarone is unavoidable, thyroid status should be checked regularly as a routine and always when the patient’s clinical state deteriorates, particularly with the return of arrhythmias.

Acknowledgment

Dr Thorne was British Heart Foundation Lecturer in grown-up congenital heart disease.

References

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Circulation. 1999;100:149-154
doi: 10.1161/01.CIR.100.2.149
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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