Cardiothoracic ratio from postero-anterior chest radiographs: A simple, reproducible and independent marker of disease severity and outcome in adults with congenital heart disease

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Abstract

Objective: The wide spectrum of intracardiac anatomy and reparative surgery available for adults with congenital heart disease (ACHD) makes uniform measurement of cardiac size and disease severity challenging. The aim of this study was to assess the prognostic potential of cardiothoracic ratio, a simple marker of cardiomegaly, in a large cohort of ACHD.

Patients and setting: Chest radiographs from 3033 ACHD patients attending our institution between 1998 and 2007 and 113 normal controls of similar age were analyzed blindly.

Design: Cardiothoracic ratio derived from plain postero-anterior chest radiographs, was compared between ACHD patients and controls, different diagnostic subgroups and different functional classes. Relationship between cardiothoracic ratio and survival was assessed using Cox regression.

Results: Average cardiothoracic ratio in ACHD was 52.0 ± 7.6% (over 50% in 56.4%), significantly higher in all ACHD diagnostic subgroups compared to controls (42.3 ± 4.0%, p < 0.0001) and highest in the “complex” cardiac anatomy, Ebstein’s anomaly and Eisenmenger subgroups. Cardiothoracic ratio related to functional class, but was high even in asymptomatic patients. During a median follow-up of 4.2 years, 164 patients died. Patients with a cardiothoracic ratio > 55% had an 8-fold increased risk of death compared to those in the lowest tertile (p < 0.001). Even patients with mildly increased cardiothoracic ratio (48–55%) had an adjusted 3.6-fold increased mortality compared to the lowest tertile.

Conclusions: Cardiothoracic ratio derived from postero-anterior chest radiographs is a simple, reproducible marker, which relates to functional class and predicts independently mortality risk in ACHD patients.

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1. Introduction

Non-invasive imaging is an essential part of the diagnostic work-up and follow-up assessment of all cardiac disease. Newer techniques, such as cardiac magnetic resonance and echocardiography are nowadays routinely used, providing a wealth of information on the cardiovascular system. However, when addressing patients with congenital heart disease, application of such techniques requires a high level of expertise in both image acquisition and interpretation, especially in patients with complex cardiac anatomy. Furthermore, there is limited information on their potential prognostic value. Integration of advanced methods with simple, readily available and easy to interpret imaging techniques may be of value in everyday practice.

Chest radiography is a cheap, widely available imaging technique that provides information on cardiac size and shape as well as on extracardiac structures. The cardiothoracic ratio (CTR) is a long-accepted method of quantifying cardiac size, and carries prognostic information in acquired heart disease [1–3]. We aimed to assess the prevalence of cardiomegaly, as assessed by the CTR, in a large population of adult patients with congenital heart disease (ACHD) and investigate its potential relation to functional status and clinical outcome.
2. Methods

2.1. Study subjects

All patients attending out tertiary center undergo chest radiography on their first assessment. For all ACHD patients attending our institution, the oldest available postero-anterior chest radiograph in the period between 1999 and 2007 was analyzed in a blind fashion from clinical and demographic data. CTR was defined as the ratio of the maximal transverse diameter of the cardiac silhouette to the distance between the internal rib margins at the level of the right hemidiaphragm and expressed as percentage [3]. Normal controls were healthy individuals undergoing chest radiography as part of a routine median screening.

Clinical data for all study patients were obtained from clinical records. Patients were classified according to the principal underlying anatomic defect. Complex anatomy was defined as unrepaired double inlet/double outlet left or right ventricle, or complex pulmonary atresia. The Bethesda classification of anatomic complexity was also used to divide patients into “mild,” “moderate” or “severe” type of congenital heart disease [4]. Survival status was assessed through the National Health Service computer system, which is linked to a national database of patient survival held by the UK Office for National Statistics. Approval by the local research ethics committee was obtained. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles. Int J Cardiol 2010; 144:1–2.

2.2. Statistical analysis

Cardiothoracic ratio was compared between ACHD patients and controls, between different diagnostic subgroups and between different functional groups (defined by New York Heart Association class) using Wilcoxon’s rank sum test or Kruskal–Wallis test, as appropriate. Association between CTR and age was tested using linear regression. Cox proportional hazards regression analysis (univariate and multiple stepwise selection) was performed. To explore the functional form of the relationship between CTR as a continuous predictor and the risk of death, smoothing splines were applied in a separate Cox regression using AIC to select the degrees of freedom of the spline. Analyses were performed using an R version 2.10.1, (R Development Core Team). Proportional hazards assumptions were checked using Schoenfeld residuals and plasma glucose was used to divide patients into tertiles and the risk of death. Selection of predictors in multiple regression using AIC to select the degrees of freedom of the spline. Selection of predictors in multiple stepwise regression using AIC to select the degrees of freedom of the spline. Analyses were performed using R version 2.10.1. (R Development Core Team 2010). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, [www.R-project.org] with the packages survival and Epi. All p-values were two-sided and a p-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Patient population

Radiographs from 3033 patients were included in the study and analyzed. An additional 113 chest radiographs from healthy controls were analyzed for comparison purposes. Demographic and clinical characteristics of ACHD patients are shown in Table 1. Mean age was 32.6 ± 15.5 years, 50.9% of patients were male.

3.2. Cardiothoracic ratio in adults with congenital heart disease

Overall, 56.4% of ACHD patients had a CTR above 50%. ACHD patients had a significantly higher CTR compared to normal controls (52.0 ± 7.6% versus 42.3 ± 4.0%, p < 0.0001, Fig. 1A) and this was true for all individual diagnostic subgroups (p < 0.0001 for all). A significant difference in average CTR was also found between diagnostic subgroups (p < 0.0001). Patients with “complex anatomy”, Ebstein’s anomaly of the tricuspid valve and Eisenmenger syndrome had the highest average CTR, with 88%, 85% and 81% of patients in these groups having a ratio > 50%. The same diagnostic subgroups had the highest prevalence of a CTR > 55% (upper tertile). A higher CTR was present in patients with greater anatomic severity: a CTR > 55% was, in fact, found in 24.1% of patients with “mild” lesions, versus 34.2% in “moderate” and 41.7% in severe types of congenital heart disease. CTR increased with increasing functional class (p < 0.0001, Fig. 1B). However, even asymptomatic patients (New York Heart Association class I), had a significantly higher CTR (49.9 ± 6.8%) compared to normal controls (p < 0.0001). Patients with resting cyanosis had a significantly increased CTR compared to non-cyanotic patients (57.0 ± 7.6% versus 51.4 ± 7.4%, p < 0.0001). A significant association was also found between age and CTR (0.90 increase in CTR per 10 years increase in age, 95% CI: 0.76–1.08, p < 0.0001).

3.3. Reproducibility of cardiothoracic ratio measurements

A high degree of inter- and intra-observer reproducibility, 100 random ACHD radiographs were analyzed twice by the same observer and by two different observers. Bland–Altman plots were produced and mean difference and 95% limits of agreement with 95% confidence intervals were calculated. The repeatability coefficient (within which 95% of all differences should be included) was calculated as twice the standard deviation of the differences between measurements on the same segment. Intra-class correlation coefficients (ICC) with 95% confidence intervals were also calculated as an additional measure of intra and inter-examiner reliability.

Analyses were performed using R version 2.10.1. (R Development Core Team 2010). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, [www.R-project.org] with the packages survival and Epi. All p-values were two-sided and a p-value of less than 0.05 was considered statistically significant.

Table 1

Demographic and clinical characteristics according to underlying diagnosis.

<table>
<thead>
<tr>
<th>Classification</th>
<th>n(%)</th>
<th>Age Mean(SD)</th>
<th>Male(%)</th>
<th>Class 1(%)</th>
<th>Class 2(%)</th>
<th>Class 3(4%)</th>
<th>Cyanosis(%)</th>
<th>Cardiothoracic ratio(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>3033(100)</td>
<td>32.6±15.5</td>
<td>50.9</td>
<td>62.4</td>
<td>31.6</td>
<td>6.0</td>
<td>10.9</td>
<td>52.0±7.6</td>
</tr>
<tr>
<td>Aortic coarctation</td>
<td>305(10.1)</td>
<td>31.8±13.0</td>
<td>61.7</td>
<td>89.8</td>
<td>10.2</td>
<td>0.0</td>
<td>0.0</td>
<td>48.5±5.6</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>42(1.4)</td>
<td>29.3±16.9</td>
<td>16.9</td>
<td>83.3</td>
<td>14.3</td>
<td>2.4</td>
<td>0.0</td>
<td>48.8±6.5</td>
</tr>
<tr>
<td>Valvar/outflow tract ACHD disease</td>
<td>720(23.7)</td>
<td>31.9±16.7</td>
<td>61.7</td>
<td>73.5</td>
<td>23.1</td>
<td>3.5</td>
<td>0.6</td>
<td>49.3±6.0</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>243(8)</td>
<td>30.0±12.9</td>
<td>49.8</td>
<td>80.7</td>
<td>17.7</td>
<td>1.6</td>
<td>0.0</td>
<td>50.0±7.1</td>
</tr>
<tr>
<td>Arterial switch for TGA</td>
<td>24(0.8)</td>
<td>17.2±4.4</td>
<td>62.9</td>
<td>62.5</td>
<td>37.5</td>
<td>0.0</td>
<td>0.0</td>
<td>51.4±6.5</td>
</tr>
<tr>
<td>Mustard operation for TGA</td>
<td>88(2.9)</td>
<td>27.4±7.4</td>
<td>55.7</td>
<td>62.5</td>
<td>34.1</td>
<td>3.4</td>
<td>5.7</td>
<td>51.4±6.0</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>405(13.4)</td>
<td>37.1±20.5</td>
<td>61.0</td>
<td>36.8</td>
<td>2.2</td>
<td>0.7</td>
<td>0.7</td>
<td>51.6±7.1</td>
</tr>
<tr>
<td>Other ACHD</td>
<td>123(4.1)</td>
<td>32.3±14.2</td>
<td>48.0</td>
<td>41.7</td>
<td>3.1</td>
<td>4.1</td>
<td>4.9</td>
<td>51.8±8.1</td>
</tr>
<tr>
<td>Congenitally corrected TGA</td>
<td>157(5.2)</td>
<td>35.9±15.4</td>
<td>50.0</td>
<td>37.9</td>
<td>12.1</td>
<td>10.6</td>
<td>10.6</td>
<td>52.3±8.2</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>132(4.4)</td>
<td>33.7±14.6</td>
<td>46.2</td>
<td>68.2</td>
<td>29.5</td>
<td>2.3</td>
<td>2.3</td>
<td>53.0±6.9</td>
</tr>
<tr>
<td>Fontan procedure</td>
<td>102(3.4)</td>
<td>25.1±9.1</td>
<td>44.1</td>
<td>39.2</td>
<td>55.9</td>
<td>4.9</td>
<td>27.5</td>
<td>54.4±8.1</td>
</tr>
<tr>
<td>Tetralogy of Fallot</td>
<td>378(12.5)</td>
<td>33.9±14.3</td>
<td>57.7</td>
<td>59.5</td>
<td>37.6</td>
<td>2.9</td>
<td>4.2</td>
<td>55.8±7.2</td>
</tr>
<tr>
<td>Eisenmenger physiology</td>
<td>187(6.2)</td>
<td>35.3±13.1</td>
<td>36.9</td>
<td>2.7</td>
<td>52.9</td>
<td>44.4</td>
<td>80.7</td>
<td>56.0±7.2</td>
</tr>
<tr>
<td>Ebstein anomaly of the tricuspid valve</td>
<td>61(2)</td>
<td>36.7±14.9</td>
<td>52.5</td>
<td>44.3</td>
<td>42.6</td>
<td>13.1</td>
<td>11.5</td>
<td>57.9±7.0</td>
</tr>
<tr>
<td>Complex ACHD</td>
<td>66(2.2)</td>
<td>30.4±11.2</td>
<td>52.9</td>
<td>26.8</td>
<td>61.8</td>
<td>11.5</td>
<td>65.0</td>
<td>58.6±7.6</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association; ACHD = adults with congenital heart disease; TGA = transposition of the great arteries

Complex anatomy we defined as unrepaired double inlet/double outlet left or right ventricle, or complex pulmonary atresia.

3.4. Impact of cardiothoracic ratio on mortality

During a median follow-up period of 4.2 years, 164 patients died (mortality 1.25% per year, 95% CI: 1.06–1.46). The highest mortality was seen in the Eisenmenger (5.54% per year, 95% CI: 3.90–7.63), complex anatomy (4.12 per year, 95% CI: 2.69–6.03) and Fontan (3.68 per year, 95% CI: 2.05–6.06) subgroups.

ACHD patients with higher CTR had a significantly higher risk of death (HR 3.72 per 10% increase in CTR, 95% CI: 3.15–4.39, p < 0.0001). When exploring the functional form of the relationship between CTR and death, the hazard of death appeared to increase constantly with increasing CTR, with no obvious threshold effects (Fig. 2). When CTR was considered as a categorical variable, patients both in the highest (CTR >55%) and middle tertile (48–55%) had a significantly higher hazard of death compared to patients in the lowest tertile (Table 2). Seven-year mortality in the highest tertile was 17.6% versus 4.7% in the middle and 1.1% in the lowest tertile (Log-rank p < 0.0001 for all, Fig. 3).

After adjustment for all univariate predictors of outcome including age, New York Heart Association functional class, cyanosis, anatomic severity and drug therapy (with diuretics, warfarin, angiotensin converting enzyme inhibitors/angiotensin receptor blockers, beta-blockers or digoxin), a CTR exceeding 55% carried an adjusted 8.5-fold increased risk in mortality compared to a CTR <48% (HR 8.48, 95% CI: 3.65–19.75, p < 0.0001). Even a mild increase in CTR (48–55%, middle tertile), carried a 3.6-fold increase in mortality (HR 3.62, 95% CI: 1.52–8.66, p = 0.004) compared to the lowest tertile.

4. Discussion

An increased CTR was encountered in all types of ACHD compared to normal controls. Cardiomegaly (CTR >50%) was present in 1 out of 2 ACHD patients, reaching 88% in patients with complex cardiac anatomy, 85% in Ebstein’s anomaly of the tricuspid valve and 81% in patients with Eisenmenger syndrome. The hazard of death increased with increasing CTR and was 8-fold in patients with a CTR >55% and 3-fold even in patients with mildly increased cardiac size (CTR = 48–55%) compared to the remainder (CTR <48%).

4.1. Cardiomegaly in ACHD

ACHD includes a wide spectrum of defects, which often result in right and/or left heart overload (pressure and/or volume) and, in turn, enlargement of one or more cardiac chambers [5–6]. Widespread cardiomegaly reflective of the latter was present in our

Table 2

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA 2</td>
<td>2.52</td>
<td>1.62–3.91</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA 3</td>
<td>3.46</td>
<td>1.95–6.14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>NYHA 4</td>
<td>9.28</td>
<td>3.46–24.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>2.26</td>
<td>1.58–3.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cardiomegaly ratio 48–55%</td>
<td>3.60</td>
<td>1.51–8.60</td>
<td>0.004</td>
</tr>
<tr>
<td>Cardiomegaly ratio &gt;55%</td>
<td>8.42</td>
<td>3.62–19.60</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

NYHA = New York Heart Association.

* Use of diuretics included as a stratum to account for violation of proportional hazards assumption.
study. The highest CTR was seen with "complex" anatomy, Ebstein’s anomaly of the tricuspid valve, Eisenmenger physiology, tetralogy of Fallot and Fontan circulation. Ebstein’s anomaly, for example, represents a model of volume overload of the right heart. Apical displacement of the tricuspid valve and tricuspid regurgitation lead to progressive dilatation of the right atrium and ultimately of the right ventricle with resultant reduced cardiac output and right heart failure. Typically, a wall to wall heart with massive cardiomegaly is the extreme end of the spectrum of this lesion [7]. Eisenmenger complex is another model, which represents a spectrum of anatomic lesions unified by pulmonary arterial hypertension and right ventricular hypertrophy developing after a phase of left to right shunting in childhood. Cardiomegaly in the Eisenmenger setting reflects atrial and/or ventricular dilatation – leading ultimately to ventricular failure – and is an ominous sign. Fontan patients, mostly of the atrioventricular type in our cohort, are a model of univentricular circulation palliated with direct anastomosis of the right atrium to the pulmonary artery. While this remarkable concept and physiology separate the pulmonary from the systemic circulation, thus relieving cyanosis, it leads to progressive right atrial dilatation and hypertrophy and, ultimately, right-sided heart failure. Cardiomegaly is, however, also seen in less complex patients with a biventricular circulation and prior successful repair. Pulmonary regurgitation is exceedingly common in patients with tetralogy of Fallot, leading to right ventricular dilatation, whereas residual pulmonary stenosis may lead to right ventricular hypertrophy and in turn right atrial dilatation [8,9]. Patients after repair of atrioventricular septal defect often present with left atrioventricular valve regurgitation, causing volume overload and dilatation of the left ventricle. Any degree of cardiomegaly seen on CTR is important in ACHD, especially when right ventricular dilatation is involved due to the geometry and anterior orientation of the right ventricle.

Cardiomegaly was present even in patients with “simple” ACHD defects. Approximately one half of patients with atrial or ventricular septal defects had a CTR exceeding 50% in this study. Late closure of large atrial septal defects is often associated with incomplete reverse right heart remodeling, explaining persisting cardiomegaly despite a reduction in CTR. Small ventricular septal defects not requiring closure in infancy may also cause left atrial and ventricular volume overload and dilatation with time. This is not uncommon during adulthood when left to right shunting tends to increase in keeping with an age-related reduction in left ventricular compliance [10,11]. Any longstanding heart chamber dilatation and ensuing hypertrophy may, in turn, provoke or exaggerate arrhythmia begetting further chamber enlargement.

4.2. The relation between cardiac size and functional capacity in ACHD

A strong relationship between CTR and functional capacity was observed in our patients. However, cardiomegaly was present even amongst asymptomatic patients, one half of whom had evidence of cardiomegaly on chest X-ray. Subjective assessment of functional status based on symptoms alone has been recently shown to be potentially misleading in ACHD, underestimating the true extent of functional limitation when objectively assessed by cardiopulmonary exercise testing [12,13]. The lifelong nature of congenital heart disease and the slow progression of hemodynamic lesions coupled with multiple adaptive mechanisms, such as chamber dilatation and hypertrophy, are primarily responsible for this discordance. Chest radiography may, therefore, have a significant role in assessing the severity of ACHD patients and assisting long-term management.

4.3. The relation of cardiac size and outcome

As discussed, enlargement of cardiac chambers reflects a number of pathological processes that affect cardiovascular function and, thus, outcome. Left ventricular hypertrophy, dilatation and remodeling are established markers of outcome in acquired heart disease [14–17]. Right heart enlargement carries additional predictive value to that of left ventricular dilation in acquired heart failure [18–20]. Enrollment of the left atrium is a risk factor for atrial fibrillation, stroke and death in patients with ischemic heart disease and heart failure [21–25]. Left and right ventricular size, as measured by cardiac magnetic resonance, are predictors of outcome in patients with tetralogy of Fallot, whereas progressive right ventricular dilatation has been employed as a criterion for the timing of pulmonary valve replacement in these patients [26]. Ventricular size and function are also predictive of outcome in patients with single ventricular physiology or a systemic right ventricle [27].

The prognostic power of the CTR in ACHD appears to be superior to that reported for patients with acquired heart failure or for the general population. Giamouzis et al. recently described a 35% propensity-adjusted increase in hazard of death in heart patients with a CTR exceeding 50% [28]. Hart et al. and Hemingway et al. described a 25% and 28% adjusted increase in hazard ratio for CTR >48% and >47% in the general population, respectively [29]. In our patients even small increases in cardiac size (48–55%) were associated with a 3-fold risk of death, rising to 8-fold when the CTR exceeded 55%.

No thresholds were found in the relation between CTR and death. Mortality increased with increasing cardiac size, even when the ratio was well below 50% or above 70%. The message from this study is clear: the smaller the heart the better the survival prospects for ACHD patients, irrespective of cardiac anatomy and type of previous intervention/s. Quantification of cardiac size by calculation of the CTR, rather than arbitrary cut-offs conventionally defining cardiomegaly is, therefore, advisable for these patients.

4.4. Clinical implications

Cardiac imaging is clearly an integral part of the diagnostic assessment and follow-up of ACHD. Advances in echocardiography and cardiac magnetic resonance have been complementary to clinical examination and angiography, providing unique insights on anatomy and heart function. Their in-depth application in ACHD clearly requires tertiary facilities and expertise both in terms of data acquisition and interpretation.

Assessment of cardiac size by chest radiography is a simple, cheap and reproducible method, with important prognostic implications. Chest radiographs are easily obtainable in almost any health care facility, primary, secondary or tertiary. Chest radiographs also provide additional information on the great arteries, lung parenchyma and...
4. Limitations

This was a retrospective study, which included a large heterogeneous population of ACHD patients, representative of current tertiary ACHD practice. The value of a single assessment of CTR was evaluated in this study. Whether interval changes in CTR, with or without pharmacological or other catheter/surgical intervention, carry additional prognostic information, remains to be examined in future prospective studies.

5. Conclusions

CTR assessed on plain postero-anterior chest radiographs relates to functional class and is an independent predictor of death in ACHD patients. In parallel to the major contribution of advanced detailed imaging, chest radiography, and the CTR in particular, retain an important role in the assessment and prognostication of ACHD, being simple, easy to obtain and quantifiable and highly reproducible.

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