EPIDEMIOLOGY

Cardiothoracic ratio within the "normal" range independently predicts mortality in patients undergoing coronary angiography

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Objective: To determine whether cardiothoracic ratio (CTR), within the range conventionally considered normal, predicted prognosis in patients undergoing coronary angiography.

Design: Cohort study with a median of 7-years follow-up.

Setting: Consecutive patients undergoing coronary angiography at Barts and The London National Health Service (NHS) Trust.

Subjects: 1005 patients with CTRs measured by chest radiography, and who subsequently underwent coronary angiography. Of these patients, 7.3% had a CTR ≥ 0.5 and were excluded from the analyses.

Outcomes: All-cause mortality and coronary event (non-fatal myocardial infarction or coronary death). Adjustments were made for age, left ventricular dysfunction, ACE inhibitor treatment, body mass index, number of diseased coronary vessels and past coronary artery bypass graft.

Results: The risk of death was increased among patients with a CTR in the upper part of the normal range. In total, 94 (18.9%) of those with a CTR below the median of 0.42 died compared with 120 (27.8%) of those with a CTR between 0.42 and 0.49 (log rank test $p < 0.001$). After adjusting for potential confounders, this increased risk remained (adjusted HR 1.45, 95% CI 1.03 to 2.05). CTR, at values below 0.5, was linearly related to the risk of coronary event (test for trend $p = 0.024$).

Conclusion: In patients undergoing coronary angiography, CTR between 0.42 and 0.49 was associated with higher mortality than in patients with smaller hearts. There was evidence of a continuous increase in risk with higher CTR. These findings, along with those in healthy populations, question the conventional textbook cut-off point of ≥ 0.5 being an abnormal CTR.

Leading textbooks of cardiology state that a cardiothoracic ratio (CTR) ≥ 0.5 is abnormal and imply that values less than this are normal.^{1,2} This continues a convention first proposed in 1919 on arbitrary grounds, without consideration of prognosis.³ CTR as measured on a chest radiograph is associated with increased left ventricular mass. Although it is known that a CTR ≥ 0.5 is associated with a poorer prognosis,⁴⁻⁷ studies in healthy populations, such as The Whitehall Study, suggest that a CTR conventionally considered normal (< 0.5) could also predict adverse outcomes.⁸ The risk associated with many clinical variables, such as cholesterol and blood pressure, is continuous with no evidence of threshold and there is evidence that in healthy populations CTR exhibits a dose-response relationship with adverse outcomes at levels < 0.5 .⁷

We aimed to determine whether CTR, within the range conventionally considered normal, predicted mortality and coronary events (non-fatal myocardial infarction or coronary death) in patients undergoing coronary angiography.

METHODS

Study population

We used data from the Appropriateness of Coronary Revascularisation (ACRE) study, which followed up a cohort of patients who had undergone coronary angiography to investigate angina. All 4121 patients undergoing coronary angiography at the Barts and The London NHS Trust, London, UK, between 15 April 1996 and 14 April 1997, and who lived within five contiguous health authorities served by 13 hospitals, were recruited into the ACRE study. There were no exclusion criteria. Written informed consent was obtained from

patients and ethics approval was obtained from the five local Research Ethics Committees.

Chest radiograph data

In all, 1473 patients had undergone a chest radiograph before angiography and after searching the film stores of the three hospital sites within the Trust, 1180 of these were found. After exclusion of 136 anteroposterior projections and a further 39 where the CTR could not be technically measured (eg, obscured cardiac silhouette, costal margins outside film border), CTR was measured in 1005 patients. The cardiac diameters were measured blinded to patients' age, sex, ethnicity and clinical details. CTR was calculated as the ratio of the maximal transverse diameter of the cardiac silhouette to the distance between the internal margins of the ribs at the level of the right hemidiaphragm. The measurements were made using a custom-built adjustable light box with a fixed T-ruler and set-square.

Angiographic, left ventricular function and clinical data

Angiographic findings were coded by a trained coder blinded to the clinical details. Left ventricular function was measured at ventriculography. The number of diseased vessels was calculated from the severity of disease in each of the 27 coronary artery segments (as defined by the Coronary Artery Surgery Study).^{9,10} To assess reliability, two cardiologists blindly over-

Abbreviations: ACRE, Appropriateness of Coronary Revascularisation; BMI, body mass index; CTR, cardiothoracic ratio; ICD, international classification of diseases

Table 1 Age-adjusted correlates of cardiothoracic ratio at the time of coronary angiography

	CTR		p Value
	<0.42 (n = 500)	0.42–0.49 (n = 432)	
Mean (SD) age (years)	59.59 (10.4)	62.40 (9.8)	<0.001
Male, n (%)	347 (69.4)	290 (67.1)	0.777
Risk factors of coronary heart disease			
Hypertensive, n (%)	140 (28.0)	148 (34.3)	0.101
Mean (SD) height (cm)	1.68 (0.1)	1.69 (0.1)	0.131
Mean (SD) weight (kg)	73.74 (13.3)	78.71 (14.8)	<0.001
Mean SD BMI (kg/m ²)	26.08 (4.38)	27.75 (4.7)	<0.001
Ever smoked, n (%)	266 (70.7)	226 (69.3)	0.441
Diabetes, n (%)	78 (15.6)	70 (16.2)	0.655
Family history of coronary disease, n (%)	166 (46.6)	144 (46.5)	0.920
Mean (SD) total cholesterol (mmol/l)	5.71 (1.2)	5.62 (1.0)	0.392
Mean (SD) systolic BP (mm Hg)	131.9 (21.2)	129.8 (22.1)	0.041
Mean (SD) diastolic BP (mm Hg)	77.53 (12.4)	76.66 (13.6)	0.528
Clinical presentation			
ACE inhibitor treatment, n (%)	104 (21.4)	134 (31.0)	0.001
Myocardial infarction before angiogram, n (%)			
No	292 (58.4)	239 (55.3)	0.332
<12 weeks	65 (13.0)	54 (12.5)	
>12 weeks	143 (28.6)	139 (32.2)	
Angina CCS class, n (%)			
I–II	143 (28.6)	110 (25.5)	0.446
III–IV	206 (41.2)	187 (43.3)	
Previous coronary bypass surgery, n (%)	55 (11.0)	86 (19.91)	0.001
Angiographic findings			
Impaired left ventricular function, n (%)	62 (12.6)	112 (26.2)	<0.001
Coronary disease, n (%)			
Zero/minimum/moderate	145 (29.4)	107 (25.0)	0.050
1 diseased vessel	139 (28.2)	103 (24.1)	
2 diseased vessels	94 (20.1)	88 (20.6)	
3 diseased vessels/left main stem	110 (22.3)	130 (30.4)	

BMI, body mass index; BP, blood pressure; CTR, cardiothoracic ratio.

read a random subsample of 209 angiograms. The cardiologists showed good agreement with the trained coder, with statistical tests of concordance revealing weighted κ values of 0.64 and 0.63.¹¹ At the time of angiography, trained nurses used standardised recording forms to extract data from patients' case notes. Details were obtained on previous myocardial infarction, hypertension and diabetes mellitus, as well as status of smoking, family history of coronary disease, functional severity of angina (Canadian Cardiovascular Society Classification¹²), height and weight (for calculating body mass index (BMI)).

Follow-up

All patients from the original ACRE study cohort had NHS numbers from which their local health authority could be identified and used to flag them with the NHS-Wide Clearing Service and the Office for National Statistics. Details on patient clinical outcomes since index angiography were obtained from hospital case notes, the Patient Administration System from patients' local hospitals and the NHS-Wide Clearing Service. Validation of acute myocardial infarction was determined using Multinational monitoring of trends and determinants in cardiovascular disease project classifications.¹³ In all, 99% of the patients in ACRE study (using NHS numbers) were flagged for mortality at the Office for National Statistics. Notification of deaths and copies of the death certificates were provided up to 14 October 2003. Coronary mortality was defined using International classification of diseases (ICD) codes ICD-9: 410–414 and ICD-10: I20–I25.

Statistical analysis

The median CTR of 0.42 was used to split patients into two groups. Those with a CTR ≥ 0.50 were then excluded (7.3% of patients, leaving 932). Age-adjusted tests of linear trend were applied to continuous variables using the analysis of variance

whereas differences in proportions were assessed by χ^2 tests when examining baseline data across CTR groups. To analyse predictors of all-cause mortality or a coronary event (non-fatal myocardial infarction or coronary death), Cox proportional hazards multiple regression analysis was used. Incidence rates were calculated by dividing the number of events in each group by 1000 person-years of follow-up. Survival was examined with unadjusted Kaplan–Meier survival curves, with comparisons between CTR groups made with the log rank test. Hazard ratios (HRs) for coronary event were also assessed in quartiles and, using the same cut-off points derived from the ACRE study, were compared with 33-year follow-up for coronary death from Whitehall data to assess continuous risk across the range of CTR <0.5. Statistical analyses were conducted with Stata software (Release 8.2).

RESULTS

Patients were followed up for a median of 7 years. During this period, 247 (24.6%) patients died. A total of 176 (17.5%) patients had either a non-fatal myocardial infarction or a coronary death.

Characteristics of the population according to CTR

Increased heart size was associated with increased age, BMI, ACE inhibitor treatment, presence of significant stenotic coronary disease, previous bypass surgery and impaired left ventricular function (table 1).

Follow-up for clinical events

Patients with a CTR between 0.42 and 0.49 had higher all-cause mortality, with 120 (27.8%) patients dying within 7 years compared with 94 (18.9%) of those with a CTR <0.42 (unadjusted log rank test $p = <0.001$; fig 1; HR 1.36; 95% CI 1.04 to 1.78; table 2). On adjusting for potential confounders age, left ventricular dysfunction, ACE inhibitor treatment, BMI,

Figure 1 Kaplan-Meier curves for all-cause mortality according to cardiothoracic ratio (CTR).

number of diseased coronary vessels and past bypass surgery, those with a CTR between 0.42 and 0.49 remained at increased risk of death (HR 1.44; 95% CI 1.02 to 2.04).

Adjusted risk for coronary event in those with a CTR between 0.42 and 0.49 was HR 1.43, 95% CI 0.96 to 2.12 when compared with those with a CTR < 0.42. There was no difference in time to first revascularisation between the two categories of CTR. A CTR in ACRE study was linearly related to the risk of coronary event when examining data in quartiles (test for trend $p = 0.024$; fig 2) and similarly for risk of coronary death in Whitehall (test for trend $p = 0.005$; fig 2).

Excluded patients with a CTR ≥ 0.5 had a considerably greater risk of all-cause mortality (fully adjusted HR 3.22, 95% CI 1.95 to 5.32, results not shown).

DISCUSSION

CTR, an indicator of large heart size, is a simple, cheap and widely used clinical measurement. In patients undergoing coronary angiography, CTR between 0.42 and 0.49 was

Numbers of coronary outcomes on follow-up in Whitehall and ACRE cohorts (years of follow-up)				
CTR	<0.38	0.38-0.42	0.42-0.46	0.46-0.49
Whitehall (33 years)	16	51	109	63
ACRE (6 years)	32	46	56	29

Figure 2 Age-adjusted HRs for coronary outcomes in Appropriateness of Coronary Revascularisation and original Whitehall studies by cardiothoracic ratio (CTR).

associated with higher mortality than in patients with smaller hearts. There was no evidence of a threshold of future risk, with a gradient of increasing risk being observed at these values of CTR < 0.5, a pattern similarly observed in the healthy population of the Whitehall Study. This is the first demonstration that a CTR conventionally defined as “normal” has an adverse prognosis in patients with coronary disease. These findings, along with those already found in healthy populations such as the Whitehall Study⁸ question the conventional textbook cut-off point of an abnormal CTR being ≥ 0.5 .

Pathophysiological considerations for CTR

CTR as measured on a chest radiograph is associated with increased left ventricular mass.¹⁴ An increase in left ventricular mass predicts a higher incidence of clinical events, including death, attributable to cardiovascular disease,¹⁵ this risk increases incrementally and is not confined to those above an arbitrary cut-off point. In clinical practice, techniques to measure left ventricular hypertrophy differ from those used to measure left ventricular mass.¹⁶ Thus, although definitions of left ventricular hypertrophy remain categorical, it seems appropriate that left ventricular mass should be treated as a continuous variable without categorising it as either normal or abnormal. Left ventricular mass may independently contribute to coronary risk through increased oxygen demand and reduced coronary reserve, impaired endocardial autoregulation and possibly small-vessel disease.¹⁷

Clinical implications

In our study, 50% of the study population had a CTR ≥ 0.42 . Thus, there is a high prevalence of “at risk” heart size. Left ventricular hypertrophy is common in healthy populations.^{18, 19} In patients with stable angina, one study reported that 13% of all chest radiographs showed cardiomegaly, whereas left ventricular hypertrophy was detected in 32% of ECGs.²⁰ Although MRI represents the current gold standard for measurement of left ventricular mass, measures like the CTR are potentially more cost-effective. Hence, CTR as calculated from the chest radiograph may act as an adjunct to management decisions in the clinical setting.

Therapeutic potential

It is unclear whether reducing measures of cardiac size positively influences prognosis. It is known that drug treatment of hypertension through ACE inhibition or angiotensin-receptor blockade leads to a reduction in CTR²¹ and left ventricular hypertrophy.²² In essential hypertension, a reduction in left ventricular mass during treatment is a favourable prognostic marker that predicts a lesser risk for subsequent cardiovascular morbid events,²³ whereas in patients with baseline ECG left ventricular hypertrophy in addition, lower left ventricular mass during antihypertensive treatment was associated with lower rates of clinical end points, additional to effects of blood pressure lowering and treatment modality.²⁴

Limitations

Routine or screening chest radiography in coronary disease is becoming less widely performed. More accurate techniques of measuring left ventricular mass such as MRI are also becoming more widely available.

Larger scale studies are required to investigate whether CTR influences other less common clinical outcomes.

CONCLUSIONS

In our study, CTR predicted all-cause mortality in a population with coronary disease with conventionally defined normal heart sizes. These findings, along with those in healthy

Table 2 Numbers, rates and HRs for deaths by cardiothoracic ratio

CTR	Number of events	Rate/1000 person-years (95% CI)	HR (95%CI) (age-adjusted)	HR (95%CI) (Fully adjusted for potential confounders)*
<0.42	94	30.02 (24.52 to 36.74)	1	1
0.42–0.49	120	47.67 (39.86 to 57.01)	1.36 (1.04 to 1.78)	1.44 (1.02 to 2.04)

CTR, cardiothoracic ratio.

*Full model—age, left ventricular dysfunction, ACE inhibitor treatment, body mass index, number of diseased coronary vessels and past coronary artery bypass graft.

populations, question the conventional textbook cut-off point of an abnormal CTR ≥ 0.5 , and suggest the potential prognostic importance of more detailed characterisation.

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