Cardiovascular Topics

Correlation between carotid intima–media thickness and patient outcomes in coronary artery disease in central South Africa

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Abstract

Objectives: Carotid intima–medial thickness (CIMT) is a non-invasive tool used to detect atherosclerosis and diagnose cardiovascular disease. This study aimed to determine whether pre-operative CIMT measurements correlated with intra- and postoperative outcomes in patients with acute coronary syndrome (ACS) undergoing coronary artery bypass graft (CABG) surgery.

Methods: This retrospective, analytical cohort included 89 patients diagnosed with ACS who received CABG surgery. Patients were divided into two cohorts: group 1: normal CIMT < 0.07 cm and group 2: abnormal CIMT ≥ 0.07 cm. B-mode ultrasound was used to measure the CIMT in all patients. Pre-, intra- and postoperative data and complications were recorded for each patient.

Results: The study included 77 (86.5%) males and 12 (13.5%) females. Pre-operative mean body mass index was significantly higher ($p = 0.03$) in group 2 than in group 1. Group 2 had a significantly increased incidence of diabetes ($p = 0.008$) and hypertension ($p = 0.009$), and increased NT-proBNP levels ($p = 0.02$). Intra- and postoperative outcomes between the groups were comparable, with no significant differences.

Conclusion: The study showed no correlation between abnormal CIMT and increased adverse intra- and postoperative patient outcomes. Therefore, the results of this study show CIMT should not be considered a tool to predict adverse events in patients undergoing CABG surgery.

Keywords: carotid intima–media thickness, acute coronary syndrome, outcomes, complications, coronary artery bypass graft surgery

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Global cardiovascular deaths are estimated at 17.9 million annually, representing 31% of all deaths.[1] In sub-Saharan Africa (SSA), non-communicable diseases are the second most common cause of death, accounting for 2.6 million deaths or 35%.[2] From the year 2000 to 2016, SSA experienced a 37% increase in coronary heart disease, with a projected increase of 21% by 2030.[3] The early detection of high-risk individuals has significant clinical value.

Measurement of carotid intima–medial thickness (CIMT) has been used as a marker to establish the presence,[4] risk[5] and extent[6] of cardiovascular disease (CVD). Several studies have validated the application of this imaging technique because it can detect slight changes over time, associated with future cardiovascular events.[7,8]

The 2010 American Heart Association/American College of Cardiology guidelines recommended measurement of CIMT as a class IIa (reasonable to perform) recommendation for cardiovascular risk assessment in asymptomatic adults with intermediate cardiovascular risk.[9] The Mannheim Carotid Intima–Media Thickness and Plaque Consensus update from the advisory board of the Watching the Risk symposium in 2004 stated that CIMT and the measurement of plaque presence are recommended for the initial detection of CVD risk in asymptomatic patients at intermediate risk or if risk factors were present. Several authors[10,11] have investigated the correlation between CIMT and an increased risk for the development of coronary artery disease (CAD) and concluded that, with an increase in CIMT, the risk of CAD and myocardial infarction becomes correspondingly higher.

Cardiac surgery with cardiopulmonary bypass (CPB) causes the systemic inflammatory response syndrome (SIRS), of which two to 6% of cases are associated with severe morbidity and death.[12] Lactate production is a well-established indicator of tissue perfusion and regional brain oxygen saturation[13] during CPB.[14] Atherosclerosis adversely affects the endothelium and is associated with an abnormal inflammatory response.[15-17] Since the mechanism of SIRS is linked to the endothelial response during CPB circulation, changes in endothelial function and tissue oxygenation are negatively affected by SIRS.[18]

CIMT is a valuable marker to predict the severity of coronary artery atherosclerosis; it may be postulated that CIMT can be used to predict surgical outcomes. Limited data are available on CIMT and its correlation with operative outcomes in coronary artery bypass graft (CABG) patients,[19,20] with no data being available for the central South African population. The aim of this study was to investigate whether pre-operative CIMT measurements in acute coronary syndrome (ACS) patients undergoing elective CABG surgery would affect intra- and postoperative surgical outcomes.

Methods

This retrospective, analytical cohort included ACS patients who received elective CABG surgery as the mode of treatment between 2008 and 2014. During this period, 200 patients received CIMT evaluations, of whom 89 patients met the inclusion criteria and had complete data sets.

The study was performed at the Cardiothoracic Surgery Department at Universitas Academic Hospital, Bloemfontein, the only public tertiary referral hospital in the central South African region. It mainly services patients from the Free State and Northern Cape provinces and Lesotho.

Ethical clearance was obtained from the Health Science Research Ethics Committee (HSREC) of the University of the Free State (UFS-HSD 2020/1708/2601) and the Free State Department of Health. This study was a sub-study of a prospective investigation conducted on all ACS patients (ETVOS NR 51/07).

Eighty-nine patients were included in the study and divided into two cohorts as per gender-specific CIMT reference ranges. Group 1 included patients with normal CIMT values (CIMT < 0.07 cm) and group 2 patients had abnormal CIMT values (CIMT ≥ 0.07 cm).

Patient demographics, clinical history, pre-operative risk factors, EuroSCORE II, CPB, near-infrared spectroscopy (NIRS) and post-operative outcomes and complications were recorded from the patients' medical records and the departmental database. Ethnicity was self-identified and cross-referenced using the hospital identification system.

Pre-operative results for levels of cholesterol, creatine, total creatine kinase, glucose, insulin, N-terminal-pro-B-type natriuretic peptide (NT-proBNP) and the creatinine kinase-MB (CK-MB) isoform were captured. Blood analysis was performed by the National Health Laboratory Service according to the laboratory standard operating procedures, applying local laboratory reference ranges for each parameter.

Body mass index (BMI) was calculated using the Du Bois formula[21] and categorised as underweight (> 18.5 kg/m^2), normal or healthy weight (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2) and obese (> 30 kg/m^2).[22]

Hypertension was defined as isolated systolic hypertension (> 140/90 mmHg), according to the definition of Mancia *et al.*[23] Patients with normal (120–129/80–89 mmHg) and/or high normal (130–139/85–89 mmHg) blood pressures were classified as not having hypertension.

The CIMT measurements were performed pre-operatively one day prior to surgery. Patient positioning and the examination procedure were done according to standardised methods published in the Mannheim CIMT and plaque consensus.[24] Standard equipment included a high-resolution B-mode system operating in black-and-white mode, with linear ultrasound transducers at frequencies > 7 MHz. A Phillips EnVisor sonar machine and phased/sector array 2–8 MHz L12-3 sonar probe was used to obtain the CIMT images. Three CIMT measurements were recorded and averaged.

For our study, a normal CIMT cut-off was set at < 0.07 cm for males and < 0.065 cm for females. For an abnormal CIMT the cut-off was ≥ 0.07 cm for males and ≥ 0.065 cm for females. Since there are no consistent reference guidelines for CIMT cut-off in the literature, the groups were divided based on the primary cut-off values per gender, as Youn *et al.* recommended.[25]

Due to the lack of standard reference guidelines in the literature, a second limited sub-analysis was done using a cut-off CIMT value of ≥ 0.09 cm as abnormal, irrespective of gender or age.[26] However, only the intra- and postoperative outcomes and complications were compared between groups.

Lactate levels were analysed at specified time intervals: (1) after the insertion of an intra-arterial catheter (T1 or baseline), (2) after intubation (T2), and (3) at approximately 15-minute intervals for the duration of surgery (T3, T4, etc). Post-operatively, lactate values were recorded at one, two, four, eight, 12, 24, 48 and 72 hours after the patient was admitted to the intensive care unit (ICU). Only peak lactate values were used for intra- and postoperative analysis. This study defines peak lactate as > 4 mmol/dl during and after surgery.

Two NIRS electrodes were placed on the patient's forehead before the patient was induced, and baseline values were set. Results were interpreted as either satisfactory (NIRS values > 50% or < 20% drop from baseline) or as compromised cerebral blood flow (NIRS values ≤ 50% or > 20% drop from baseline). It should be noted that not all patients received NIRS measurements because not all theatres were equipped with a NIRS monitor. Only 32 of the 89 patients had recorded NIRS measurements.

Standard transthoracic echocardiograms (TTE) were performed on all patients in line with the British Society of Echocardiography protocol for comprehensive adult TTE studies.[27] A Phillips EnVisor echocardiography machine was used and the patient's left ventricular ejection fraction (LVEF) was calculated peri-operatively using Simpson's method. The American Society of Echocardiography defines LVEF as the percentage of blood ejected during a left ventricular contraction of the heart, using quantitative measures. LVEF was calculated using the formula:

$$\text{LVEF} = \frac{\text{EDV} - \text{ESV}}{\text{EDV}} \times 100$$

Where EDV is the end-diastolic volume and ESV is the end-systolic volume. The cut-off value for normal LVEF for our study was determined at > 55%.

Statistical analysis

Statistical analyses were done using R Software version 3.2.2 (2015/08/14). XLSTAT version 2016.03.30846 was used for *t*-tests and the calculation of confidence intervals. Data were compared using the Student's *t*-test for normally distributed continuous variables, the Mann–Whitney test for continuous data that were not normally distributed, and the chi-squared or Fisher's exact test (where cell counts were less than five) for categorical variables. Statistical significance was noted if the *p*-value was less than 0.05.

Table 1. Demographic and anthropometric data of normal and abnormal CIMT groups

Variables	*Group 1 normal CIMT* (n = *28, 31%*)	*Group 2 abnormal CIMT* (n = *61, 69%*)	p-*value*
Age (years), mean ± SD	58.9 ± 8.88	59.6 ± 9.15	0.72
Gender, *n* (%)			
Male	23 (82.1)	54 (88.5)	
Female	5 (17.9)	7 (11.5)	
Ethnicity, *n* (%)			
Caucasian (*n* = 69)	22 (78.57)	47 (77.05)	> 0.99
Mixed race (*n* = 9)	2 (7.14)	7 (11.48)	0.71
Black African (*n* = 9)	4 (14.29)	5 (8.20)	0.45
Asian (*n* = 2)	0	2 (3.28)	–
BMI (kg/m²), mean ± SD	26.6 ± 4.88	29.2 ± 5.85	0.03*
Overweight, *n* (%)	12 (42.9)	19 (31.2)	
Obese, *n* (%)	13 (46.4)	16 (26.2)	
Severely obese, *n* (%)	0	4 (6.6)	

Normal CIMT males < 0.07 cm; abnormal CIMT males ≥ 0.07 cm; normal CIMT females < 0.065 cm; abnormal CIMT females ≥ 0.065 cm. CIMT, carotid intima–media thickness; SD, standard deviation.
*Statistically significant *p*-value < 0.05

Results

Eighty-nine ACS patients received CIMT measurements prior to elective CABG surgery. Twenty-eight patients (31%) presented with a normal CIMT and 61 (69%) with an abnormal CIMT. Seventy-seven (86.5%) were male and 12 (13.5%) were female patients. The mean age of the groups was comparable, and both groups presented with a preponderance of Caucasian males (80%). The mean BMI was significantly higher in group 2 compared to group 1 (29.2 vs 26.6 kg/m²) ($p < 0.05$). The demographic and anthropometric data are summarised in Table 1.

Significantly more patients in group 2 with an abnormal CIMT presented with hypertension ($p = 0.009$), diabetes ($p = 0.008$) and an increased NT-proBNP level ($p = 0.017$). Low-density lipoprotein cholesterol could not be analysed due to incomplete data sets. All other clinical parameters were comparable between groups ($p > 0.05$). The pre-operative CK-MB isoform, total cholesterol and NT-proBNP values exceeded the upper reference limit in group 2 (Table 2). The mean EuroSCORE II of both groups was high, but patients were evenly distributed in the three severity classifications with no differences between groups.

Table 2. Pre-operative clinical data of normal and abnormal CIMT groups

Variables	*Group 1 normal CIMT* (n = *28, 31%*)	*Group 2 abnormal CIMT* (n = *61, 69%*)	p-*value*
CIMT (mm), mean ± SD	0.06 ± 0.01	0.095 ± 0.03	< 0.0001*
Hypertension, *n* (%)	16 (57.14)	52 (85.25)	0.009*
Diabetes, *n* (%)	2 (7.14)	21 (34.43)	0.008*
Cholesterol (LDL) > 3 mmol, *n* (%) mean ± SD	24 (85.71) 4.4 ± 0.07)	28 (45.90) 4.09 ± 0.94	No analysis, incomplete data sets
Statins use, *n* (%)	22 (78.57)	44 (67.21)	–
Hypercholesterolaemia, *n* (%)	14 (50.0)	24 (39.34)	0.57
NT-proBNP (ng/l), mean ± SD	562.9 ± 591.2	1344.4 ± 1646.7	0.017*
Current/ex-smoker, *n* (%)	12 (42.86)	31 (50.82)	0.64
CK-MB isoform (ng/ml), mean ± SD	32.8 ± 96.39	20.8 ± 49.28	0.58
Glucose (mmol/l), mean ± SD	6.05 ± 2.053	6.37 ± 2.70	0.58
Insulin (mU/l), mean ± SD	24.8 ± 39.49	28.06 ± 30.71	0.74
LVEF, mean ± SD	54.4 ± 14.39	52.2 ± 15.07	0.52
EuroSCORE II, *n* (%)	6 (21.4)	16 (26.2)	–
0–2, low risk, *n* (%)	11 (39.3)	20 (32.8)	–
3–5, medium risk, *n* (%)	7 (25.0)	20 (32.8)	–
> 5, high risk, mean ± SD	6.18 ± 9.60	7.53 ± 13.85	0.61

Normal CIMT males < 0.70 mm; abnormal CIMT males ≥ 0.07 cm; normal CIMT females < 0.065 cm; abnormal CIMT females ≥ 0.065 cm.
CIMT, carotid intima–media thickness; SD, standard deviation; LVEF, left ventricular ejection fraction.
*Statistically significant *p*-value < 0.05.

Table 3. Intra-operative clinical data of normal and abnormal CIMT groups

Variables	*Group 1 normal CIMT* (n = *28, 31%*)	*Group 2 abnormal CIMT* (n = *61, 69%*)	p-*value*
Peak lactate (mmol/dl), mean ± SD	4.7 ± 1.6	4.02 ± 1.8	0.085
Cumulative bypass time (min), mean ± SD	112 ± 22.7	111.4 ± 31.5	0.92
Cumulative cross-clamp time (min), mean ± SD	60.5 ± 14.3	59.3 ± 18.5	0.75
Total number of grafts ≥ 3, *n* (%)	21 (75.00)	43 (70.5)	0.85
Intra-aortic balloon pump, *n* (%)	15 (53.6)	21 (34.4)	0.14
NIRS > 50%; drop of < 20%, *n* (%)	3 (10.7)	17 (27.9)	0.13
NIRS < 50%; drop of > 20%, *n* (%)	13 (46.5)	24 (39.3)	
Phenylephrine bolus at 100 µg/ml during bypass, *n* (%)	23 (82.1)	49 (80.3)	> 0.99
mean ± SD	15.07 ± 22.04	20.7 ± 17.8	0.30
Adrenaline during anaesthesia at more than 20 µg/kg/min, *n* (%)	6 (21.4)	9 (14.8)	0.63
mean ± SD	0.07 ± 0.04	0.3 ± 0.4	0.16
Adrenaline bolus during bypass 1:1 000 000 mg/ml, *n* (%)	4 (14.3)	17 (27.9)	0.20
mean ± SD	3 ± 1.8	7 ± 9.4	0.13
Effortil bolus during bypass (mg), *n* (%)	2 (7.1)	5 (8.2)	> 0.99
mean ± SD	14.5 ± 7.8	11.6 ± 5.4	0.69

Normal CIMT males < 0.07 cm; abnormal CIMT males ≥ 0.07cm; normal CIMT females < 0.065 cm; abnormal CIMT females ≥ 0.065 cm. CIMT, carotid intima–media thickness; SD, standard deviation.
*Statistically significant *p*-value < 0.05.

The intra-operative clinical variables were similar between groups and no significant differences were detected (Table 3). The post-operative outcomes between groups were similar with no significant differences (Table 4).

Most patients in both groups had an ICU stay of less than three days, with only 21.43% in group 1 and 14.75% in group 2 exceeding a three-day ICU stay. The mortality rate was low, with only one (2%) fatality in the abnormal CIMT group due to sepsis.

Postoperative complications in both groups were limited. Patients with an abnormal CIMT tended to have more postoperative complications than those with a normal CIMT

Table 4. Post-operative outcomes of normal and abnormal CIMT groups

Variables	*Group 1 Normal CIMT* (n = *28, 31%*)	*Group 2 Abnormal CIMT* (n = *61, 69%*)	p-*value*
Peak lactate (> 4 mmol/dl), mean ± SD	5.3 ± 3.4	5.8 ±3.2	0.52
Length of stay in ICU > 3 days, mean ± SD	3.1 ± 0.7	3.13 ± 2.2	0.63
n (%)	6 (21.4)	9 (14.8)	
Length of stay in ICU > 3 days, mean ± SD	2.94 ± 0.1	3.54 ± 0.6	0.33
Mortality, *n* (%)	0 (0)	1 (2)	–

Normal CIMT males < 0.07 cm; abnormal CIMT males ≥ 0.07 cm; normal CIMT females < 0.065 cm; abnormal CIMT females ≥ 0.065 cm.
CIMT, carotid intima–media thickness; SD, standard deviation.
*Statistically significant *p*-value < 0.05.

Table 5. Pre-, intra- and postoperative outcomes compared to normal (< 0.09 cm) and abnormal (≥ 0.09 cm) CIMT values regardless of gender

Variables	*Group 1 normal CIMT < 0.09 cm (n = 61, 68.5%)*	*Group 2 abnormal CIMT ≥ 0.09 cm (n = 28, 31.5%)*	p-*value*
Pre-operative clinical data, mean ± SD			
NT-proBNP (ng/l),	936.1 ± 165.7	1391 ± 650.5	0.51
LVEF	53.6 ± 1.7	52.1 ± 3.3	0.69
CK-MB isoform (ng/ml)	21.8 ± 10.3	36.10 ± 27.9	0.62
Intra-operative clinical data, mean ± SD			
Peak lactate (mmol/dl)	4.3 ± 0.2	3.9 ± 0.4	0.29
Cumulative bypass time (min)	112.9 ± 3.8	109.6 ± 6.6	0.66
Postoperative outcomes, mean ± SD			
Peak lactate (> 4 mmol/dl)	5.8 ± 0.4	5.69 ± 0.70	0.93

Normal CIMT < 0.09 cm; abnormal CIMT ≥ 0.09 cm.
CIMT, carotid intima–media thickness; SD, standard deviation.
*Statistically significant *p*-value < 0.05.

(34.4 vs 21.4%) (Fig. 1). The prevalence of postoperative complications was too low to analyse statistically.

When a higher CIMT cut-off value was used as an abnormal indicator for CIMT (0.09 cm), the pre-, intra- and postoperative limited sub-analysis demonstrated similar results between groups with no statistically significant differences (Table 5). Postoperative complications did not show any significant differences.

Discussion

This study aimed to assess the impact of an abnormal CIMT on intra- and postoperative variables in ACS patients receiving CABG surgery. It was hypothesised that patients with pronounced/thickened CIMTs would present with worse intra- and postoperative measurable abnormalities, outcomes and complications. The study results showed that patients with abnormal CIMTs had more pre-operative risk factors than patients with normal CIMTs. However, no significant differences were observed between intra- and postoperative variables when comparing the normal and abnormal CIMT groups, even at a higher abnormal CIMT cut-off value of ≥ 0.09 cm.

The anthropometric analysis showed that patients with an abnormal CIMT had a significantly higher BMI and were significantly more overweight than patients with a normal CIMT. This finding is in agreement with studies conducted by Rashid and Mahmud[28] and El Jalbout *et al.*,[29] who reported an increased CIMT in adolescents with an increased BMI.

In this cohort, 69% of ACS patients who required CPB surgery due to severe CAD had an abnormal CIMT. This finding concurs with several other studies that concluded that CIMT is elevated with advanced CAD.[6,30]

In our study, in patients with an abnormal CIMT, risk factors such as hypertension, diabetes and increased NT-proBNP levels were significantly more frequent than in those with a normal CIMT. Diabetes directly impacts on CIMT due to vascular endothelial dysfunction.[31] Baba *et al.* reported that patients presenting with diabetes had higher CIMT values than healthy controls and that the prevalence of increased CIMT was very high (82.8%) in the Nigerian population.[31] In our study, 34% of patients with diabetes had abnormal CIMTs, significantly more than patients with normal CIMTs.

Hypertension is multifactorial in cause, including but not limited to, high sodium intake, cigarette smoking, unhealthy diet, low potassium intake, lack of physical activity[32] and family history of hypertension.[33] Evidence suggests that hypertension is strongly associated with increased CIMT thickening.[34] The carotid artery has a relatively small media compared with muscular arteries. Therefore an increased CIMT is thought to primarily represent intimal rather than medial thickening, supporting atherosclerosis-related cardiovascular events rather than hypertrophy of the medial layer of the carotid artery.[35]

Our results (Table 2) showed an association between hypertension and an increased CIMT, with significantly more patients presenting with hypertension in the abnormal CIMT group (85.25%) compared to the normal CIMT group (57.14%). Similar observations were reported by Rashid and Mahmud, Magnussen, and Chen *et al.*[28,35,36]

The MONICA Risk, Genetics, Archiving, and Monograph (MORGAM) biomarker project demonstrated that adding

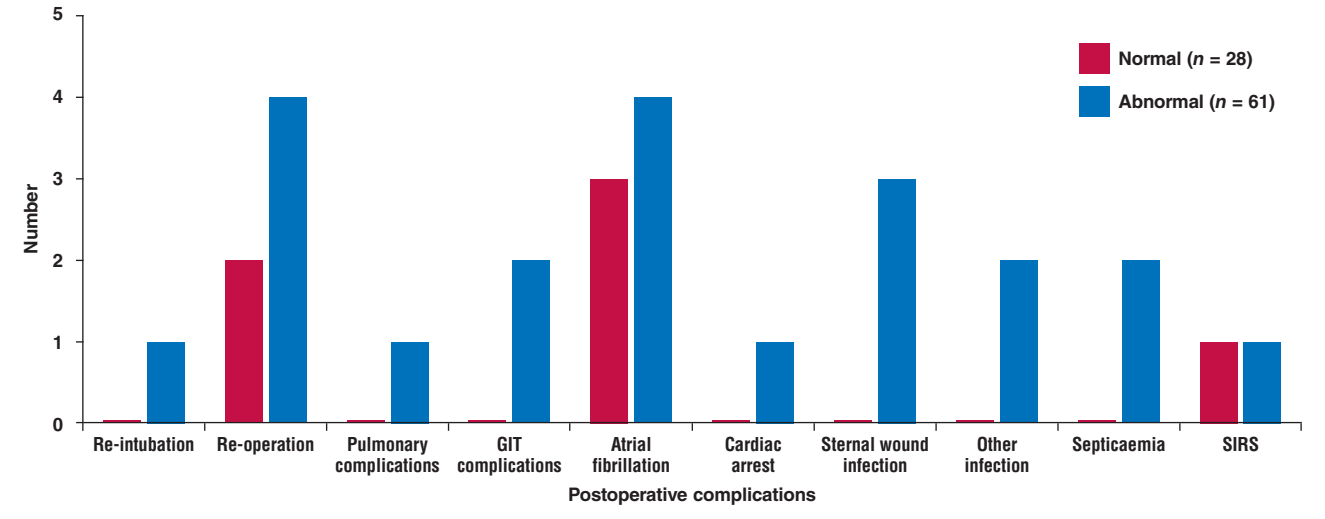

Fig. 1. Post-operative complications of normal and abnormal CIMT groups.

NT-proBNP to a conventional risk model can improve a 10-year risk estimation for cardiovascular events.[37] This study showed that NT-proBNP was significantly higher pre-operatively in patients with an abnormal CIMT. A response to left ventricular strain or ischaemia causes a release of NT-proBNP, which has been found to be an important biomarker for left ventricular systolic dysfunction and left ventricular stress in the general population.[38]

There was no correlation between CIMT and intra-operative factors, even when a higher abnormal CIMT cut-off value was used. A possible reason is that the study population was too small and that subtle differences may not have been detected. Interestingly, no difference in lactate values was found between the groups. Insufficient oxygen delivery and hypoperfusion during CPB contribute to hyperlactataemia.[39] CIMT is a marker of subclinical atherosclerosis and endothelial dysfunction,[40] which is a factor that would increase lactate production intra-operatively due to the systemic inflammatory response caused by CPB.[41] An increase in lactate is associated with poor outcomes and increased mortality rates in cardiac surgery patients.[42]

The post-operative complications were comparable between the groups with no statistically significant differences. Our study's overall post-operative complication rate was low but corresponds with the overall rate of complications reported after CABG surgery (1–3%).[43]

Data on the accepted normative values are unavailable because there is no widely accepted cut-off value for what constitutes an adverse/abnormal CIMT value. Many variables affect the thickening of the carotid intima in different populations, whether it be age, ethnicity or diet.[35] Even when using a higher abnormal CIMT cut-off value of 0.09 cm, there was no relationship between higher CIMT values and increased post-operative outcomes and complications. Our results agree with Aboyans *et al.*,[19] who also found little value in pre-operative CIMT.

By contrast, some value was reported in off-pump CABG where increased CIMT (0.9 mm) was associated with increased 30-day morbidity rates.[20] However, based on our results, CIMT should not be considered a predictor for surgical outcomes in ACS patients undergoing CABG surgery using CPB. Before criteria for abnormal CIMT can be set, there is a need for measurement consensus and population reference values. There are currently no set CIMT population values for South Africa.

This study is limited by its retrospective design and the sample size was small. For this reason, only assumptions can be made. A larger patient population may reveal more definite answers on whether increased CIMT values can predict surgical outcomes.

Conclusion

Our study demonstrated an association between abnormal CIMT and pre-operative risk factors such as BMI, diabetes, hypertension and NT-proBNP level. However, there was no correlation between abnormal CIMT and an increased rate of adverse intra- and postoperative patient outcomes. Therefore, our study does not support the use of CIMT to predict adverse events in patients undergoing CABG surgery. Further studies that include larger patient numbers are needed to confirm our observations.

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