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Breaking Female Hearts: The Gender Gap in Cardiovascular Research

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INTRODUCTION

Cardiovascular disease is the biggest killer of both men and women, causing 17.5 million deaths combined in 2012,1 which is expected to rise to 23.4 million by 2030.2 The leading cause of death in both sexes is ischemic heart disease, with hypertensive heart disease also appearing in the top ten and vascular complications the majority of the remainder.1 Notably, mortality rates are increasing more rapidly in younger women compared to men.3 Given these observations, it might be expected that our knowledge of the cardiovascular system and treatment of its disorders would be based on studies performed on biological material and organisms of both male and female origin, in fairly equal proportions. However, this is simply not the case. In biomedical research, many publications do not specify the sex of the animals (presumably the reader should assume male), and where sex is specified the majority focus on males.4 In addition, drug studies are conducted mainly on males.5 Equal representation of men and women is also lacking in many large-scale clinical trials4,6; somewhat surprising given that women represent a rather significant proportion of patients undergoing treatment in the clinic.

WHY?

Since most studies utilising mice or rats were performed exclusively on males, this became convention. Further studies required a continued use of males in order to relate the conclusions to previous data, and has compound the issue. It may also have been assumed that the response of both sexes would be similar, thus negating the need for inclusion or use of females in any studies bar those on gender specific situations e.g. pregnancy. Another concern often mooted is that of confounding effects in females from the oestrous cycle. Very few studies have been conducted on this topic, so there is very little evidence to support this view. In fact, many support the opposite. One such study highlighted that the oestrous cycle can affect myocardial electrical and contractile function, but that females housed separately from males do not exhibit regular oestrous cycles and these changes are therefore negated to some extent.7 Thus under standard laboratory conditions, the oestrous cycle may be less relevant than assumed. Another study found that the oestrous cycle had no effect on response to ischemic injury (one of the most relevant to mortality in humans) in female rats.8 In addition, a meta-analytical study showed convincingly that in most settings (though in neuroscience rather than cardiac research), the female hormone cycle did not elicit any more variability in females than in males.9 To challenge convention, this is certainly an area that warrants further investigation in a heart specific context. Indeed, even if the oestrous cycle is found to be a significant factor should it be ignored? What if this affects factors such as presentation, symptoms and drug efficacy? This could be an important question to ask on clinical admittance to direct diagnosis and treatment in women.

Another issue is that performing studies on both sexes would require significantly more resource and investment. However, the end may justify the means. The importance of considering females at all levels; in studies at the molecular, cellular, organ and whole body level, from mice to humans, from target identification to translational therapies, is outlined below.
WHY DOES IT MATTER?

There is a clear and urgent need to consider both sexes when conducting basic research and the preclinical studies that follow. Mainly, this must be addressed due to sex-specific differences in both humans and mice. An increasing number of studies in mice demonstrate sex-specific differences in e.g. pathophysiological phenotypes, molecular mechanisms, degree of pathological response, response to drugs, and so on. All of these factors have the potential to strongly impact on the degree of success in clinical trials, and in guiding diagnosis and treatment in the clinic.

In several mouse strains where both sexes have been considered, pathological cardiac phenotypes are only evident in males, and where apparent in females, generally pathological remodelling and progression to heart failure is diminished. Cardiomyopathy induced by genetic means also appears to primarily affect males, and more severely so than females. Since cardiovascular disease affects both sexes similarly in terms of mortality in humans, these observations seem surprising. However, there are notable exceptions such as platelet-derived growth factor-C (PDGF-C) induced hypertrophy, and impaired contraction induced by overexpression of alcohol dehydrogenase, which are more pronounced in females. Interestingly, women are also more susceptible to alcohol-induced cardiac disease, suggesting that a comorbidity of alcohol abuse in women is more of a cardiovascular disease risk factor than in men. In addition, many animal studies are based on isolated stresses and female responses may be as severe as males when presented with certain comorbidities. A study this year showed that while female hearts fared better in response to ischemia, this protection was lost in hearts with pre-existing hypertrophy. Male and female hearts were found to have different calcium handling properties, and in the setting of pre-existing hypertrophic cardiomyopathy responded differently to ischemic challenges. Thus the more pronounced functional recovery to ischemia typically seen in female hearts is blunted in the case of pre-existing hypertrophy.

Drug metabolism, toxicity and efficacy can also differ significantly between males and females. In addition to presentation and outcomes, sex-specific distinctions exist in the pathophysiological mechanisms underlying cardiovascular disease. Within many heart failure models, gender also influences mortality, heart failure severity, and patterns of LV remodeling. Models of pressure overload exemplify gender differences in the patterns of hypertrophic remodelling; females are less inclined towards chamber dilatation and wall thickness increases consistent with a more compensated, concentric type of remodelling. Conversely, male hearts tend to display increased propensity towards eccentric hypertrophy.

These observations are of particular relevance to the pharmaceutical industry since translation to the clinic is poor, and costs high. That females have rarely been considered in study design as well as in basic science research and pre-clinical trials, may in fact be an extremely significant (and simple) explanation for the poor translation from mouse to human. Data from studies on male mice are applied to both male and female humans. Given the emerging wealth of evidence to suggest that pathology and drug responses both in mouse and human females can be very different, this is an inherently flawed approach. Translational potential might be enhanced by testing novel therapies in models that include both sexes. It has been noted that rodent drug studies are conducted mainly on males, while most drugs removed from the market had greater adverse effects in women than in men. With drug related cardiac toxicity being the greatest cause for withdrawal from the market, it would certainly be prudent to include testing in female models in the pre-clinical pipeline, paying particular attention to drug related toxicity in both sexes.

Despite a substantial programme of supporting experimental and preclinical evidence, the outcome from the recent CIRCUS trial (Does Cyclosporine Improve Clinical Outcome in ST Elevation Myocardial Infarction) was disappointingly negative. The reasons for this have been debated, however sex related differences have not been discussed. This study comprised over 80% males in control and treatment groups. That the targeted patient group are predominantly men suggests this to be more of a gender specific disorder, or, that diagnosis and treatment is inferior in females. Indeed, a number of studies now show that to the latter. It might be that women were underdiagnosed, and/or that the 20% of women in the CIRCUS trial responded differently to treatment and thus ‘skewed’ or masked a more positive outcome in males. It would be interesting to see whether exclusion of female participants in this case might change the overall conclusion of the study. Conversely, greater efficacy might be achieved in women than in men.

WHY ARE RESPONSES DIFFERENT BETWEEN THE SEXES?

Less severe pathological responses often seen in female mice compared to males (discussed above) have been suggested to be moderated mainly by oestrogen, which can activate cardioprotective signalling pathways such as nitric oxide synthase (NOS) and Akt. While levels of Akt do not differ, the ratio of phosphorylated Akt to total Akt is significantly higher in female than male hearts, and increases further during reperfusion in females. Conversely, in some instances, oestrogen has been shown to inhibit pathways associated in some instances with pathological progression, e.g. p38 mitogen activated kinase (MAPK), which is selectively inhibited
by estrogen over the other MAPKs c-Jun N-terminal kinase (JNK), or extracellular signal regulated kinase (ERK1/2). However, this view is becoming increasingly uncertain; though undoubtedly a factor in certain settings, in others, it is not.\textsuperscript{10,11} Further, hormone replacement therapy was found to increase cardiovascular events in postmenopausal women,\textsuperscript{26} indicating that the protective effects of oestrogen cannot be presumed.

Other pathways that may contribute to differential responses in hypertrophic and dilated cardiomyopathies include growth factors (Transforming growth factor beta; TGFβ), cytokines (Tumour necrosis factor alpha; TNFα), transcription factors (MEF2) and the hormone modulator angiotensin-converting enzyme (ACE). All are generally elevated in male hearts either in the absence of stimulation, or exhibit a greater response on pathological stimulation compared to female counterparts.\textsuperscript{10}

WHERE ARE WE HEADED?

In the United States, approximately half of the National Institute of Health (NIH) funded clinical studies include women, but this is not reflected in preceding experimental studies in cells or animals. The NIH initiated a big drive in 2014 to address this issue.\textsuperscript{21} Consideration of the role of sex and differential responses in study design had been already purported prior to this in the last decade by the European Union and the German Society of Epidemiology, followed by the Canadian Institutes of Health.\textsuperscript{4} Thus a worldwide drive to raise awareness and to support the inclusion of females in pre-clinical models and basic research is well underway. While significant impact has yet to be made, awareness and accumulation of evidence showing gender specific differences will likely influence design of preclinical studies and the basic science studies that support them in the future.

CONCLUSIONS

Given the major differences between the sexes in the underlying mechanisms of disease, along with diagnosis and treatment responses, clinical guidelines should take this into account. However, this is not currently common practice. For instance, the 2016 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure give very little distinction between the sexes.\textsuperscript{25} This is no doubt hampered by the lack of knowledge of gender specific responses in the foundation of clinical science, i.e. basic research. Even at the level of clinical trials, women are still under represented.\textsuperscript{4,6} Some treatments have the potential to give more encouraging results in one sex over the other, and influence clinical trial design to focus on the most likely group to positively respond. However, in the absence of supporting evidence, clinical trials should include equal proportions of both males and females with the data reported in a sex specific manner. Perhaps, some studies could retrospectively be assessed in this way; failure of some trials might in fact be due to different responses between genders.

The prospect of conducting research on both sexes might seem daunting in terms of extra resources required, but in the long-term may impact more positively on our knowledge of the molecular mechanisms that underlie disease, and their application to clinical treatments and outcomes. Female mice seem relatively more protected against cardiac insults, internal or external when compared to males, at least in the absence of comorbidities. This in itself could provide an avenue for further exploration of cardioprotective signalling pathways and reveal further tailored targets for pharmacological intervention that might have greater efficacy in males. Further to this, future studies could more readily be conducted on different sexes at an earlier stage, before moving into in vivo models. Isolated cardiomyocytes for in vitro studies for example, do not have to come only from males. Further, human based platforms such as patient derived induced pluripotent stem cell derived cardiomyocytes from male and female patients could provide a fruitful avenue for such studies, and drug efficacy and toxicity should certainly be tested in these types of models. On the basis of this kind of research, subsequent trials could more reasonably be focussed on models of selected at-risk female or male subgroups, most likely with enhanced translational potential.

The main question is, what are the signalling mechanisms that really underlie these differences and how can they be manipulated for more tailored treatments between men and women? Should we be thinking along the lines of personalised medicine on the basis of gender? Perhaps, on answering these questions, we can hope to bridge the gender gap in cardiovascular research.

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The Factors Causing Left Atrial Appendage Clot Formation in Patients With Severe Rheumatic Mitral Stenosis

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ABSTRACT

Background: Rheumatic mitral stenosis is still present in the developing world. Left atrial appendage clot is a common complication of mitral stenosis. The management differs significantly if there is presence of clot.

Objective: We assessed the factors responsible for left atrial appendage clot formation in patients with severe mitral stenosis through transesophageal echocardiography

Methods: An observational study was conducted among 82 (73 females, mean age 35.8±11.8 years) patients with severe mitral stenosis who underwent transesophageal echocardiography before percutaneous transmitral commissurotomy. Patients were classified into two groups based on the presence or absence of left atrial thrombus. Group 1 consisted of 24 patients (women to men ratio 9:1:9) with left atrial thrombus, while group 2 consisted of 58 patients (women to men ratio 88:12) without left atrial thrombus. Transesophageal echocardiographic findings were reviewed in all patients.

Results: There was no significant difference between the two groups in terms of age, sex, systolic pulmonary artery pressure and mitral valve mean pressure gradient (MVMPG), there was significant difference regarding frequency of atrial fibrillation (p≤0.05), left atrial size (p≤ 0.05), mitral valve area and flow velocities (p≤0.05) in group-1 patients. Similarly, atrial fibrillation was observed in 35(42.7%) patients out of which 20(83.3%) patients had thrombus in left atrial appendage.

Conclusion: The frequency of left atrial thrombus formation increased in patients with rheumatic mitral stenosis because of low left atrial appendage flow velocities, atrial fibrillation and smaller mitral valve area.

KEYWORDS: Mitral stenosis; Left atrial appendage; Thrombus; Echocardiography.

INTRODUCTION

Mitral stenosis is a huge burden in the third world countries. It has been reported that the incidence of rheumatic fever is 206/100,000 and prevalence of rheumatic heart disease is 18.6/1000. The prevalence of rheumatic heart disease (RHD) in Pakistan is also high like other third world countries and was found to be 22/1000 in inner Lahore and 5.7/1000. The most affected valve in rheumatic heart disease is mitral valve. It is solely affected in 25% and is affected in combination with other valves in 40% of patients. The symptoms develop 10 to 20 years after the disease which include chest discomfort, cough, and shortness of breath during exercise, hemoptysis and atrial fibrillation.

Mitral stenosis can lead to enlargement of the left atrium (LA) leading to increased risk of thrombus formation. The frequency of left atrial thrombi is between 20 and 33% according to the literature. Left atrial thrombus is more frequently associated with embolic events.

Left Atrial Appendage (LAA) is the common site for thrombus formation. Increasing age and severity of mitral stenosis (MS) also increase the risk of thrombus formation.
pressed LAA function has also shown to be one of the predictor of LAA clot formation.\(^1\) Left atrial thrombus can be defined as echo dense mass of any size with independent motion relative to chamber wall found in left atrial cavity or LAA.\(^1\)

The accessibility of the left atrial appendage by transesophageal echocardiography (TEE) is better than transthoracic echocardiography (TTE) for detection of clot. We designed this study to evaluate various echocardiographic predictors for LA clot in patients with severe mitral stenosis.

**ETHICS COMMITTEE APPROVAL**

Taking approval through ethical committee of The Children Hospital and Institute of Child Health, Lahore, Pakistan.

**METHODS**

In this observational study, a total of 82 patients (range from 21 to 65 years, mean age was 35.8±11.8 years) of severe mitral stenosis who were referred to perform Transesophageal echocardiography (TEE) were included before percutaneous transmial commisurotomy (PTMC). A written informed consent was obtained from all patients. Mitral stenosis was diagnosed on the basis of TEE and atrial fibrillation was demonstrated on baseline electrocardiogram. Findings of ECG and echocardiogram were document. Patients with mitral regurgitation, significant aortic valve disease, previous closed mitral valvotomy and currently taking anticoagulation or antiplatelet therapy were excluded from study.

All patients were divided into two groups based on presence or absence of thrombus. Group I consisted of 24 patients (2 men and 22 women) with left atrial thrombus. Group 2 consisted of 52 patients (7 men and 51 women) without left atrial thrombus.

**TEE examination**

A complete transthoracic echocardiographic (TTE) examination was done in all patients with a 2-5 MHz transducer. Mitral valve area was measured by continuous wave Doppler using pressure half time method.\(^3,13\) Systolic pulmonary artery pressure was measured using maximal tricuspid regurgitation velocity and applying Bernoulli equation to convert this value into pressure values. Estimated right atrial pressure was added in this value.\(^3\) To maximize the transthoracic visualization of left atrial thrombus all standard view were done along with angulations of transducer.

TEE was performed in all cases after TTE using a 9 T MHz transducer multiplane probe. All patients were given local pharyngeal anesthesia (1% lidocaine spray) and intravenous diazepam 3 mg. During the study heart rate, blood pressure, single lead ECG and pulse oximetry were monitored. TEE probe was introduced with the patient lying supine in left lateral position. The left atrium was scanned in short axis and bivacal view.\(^3\) With a counter clockwise rotation of the probe at the level of aortic valve, left atrial appendage was visualized and thrombus was diagnosed by the presence of well-defined echogenic intracavity mass having an echo texture different from that of underlying endocardium.\(^3\) All TEE were performed by trained cardiologist who had experience of more than 5 years.

**DATA ANALYSIS**

Variables like LA size, mitral valve area (MVA), mitral valve mean pressure gradient (MVMPG), LAA flow velocity, pulmonary artery systolic pressure and thrombus in LA appendage were noted on the proforma for each patient along with ECG.

**STATISTICAL ANALYSIS**

Appropriate statistical data analysis technique by using SPSS version 20 was applied. Categorical variables were described by numbers and percentages while continuous variables were described as mean and SD (standard deviations). Chi square test was applied for categorical variables and independent sample t test was applied for comparison between these two groups. A level of 5% was considered significance.

**RESULTS**

Atrial fibrillation was observed in 35 (42.7%) patients (Table 1). Atrial fibrillation was more significantly associated with thrombus formation i.e. 20 (83.3%) patients having as compared to 4 (16.7%) having sinus rhythm (Figure 1). Patients with left atrial thrombus did not differ significantly from the patients without left atrial thrombus regarding age, sex, systolic pulmonary artery pressure (SPAP) and mitral valve mean peak gradient (MVMPG) (\(p\geq0.05\)) but left atrial thrombus was found to be significantly higher in patients those had frequent atrial fibrillation (\(p\leq0.05\)), larger left atrial size (\(p\leq0.05\)), smaller mitral valve area and low flow velocities (\(p\leq0.05\)) which also indicate left atrial appendage dysfunction (Figure 2). Table 2 shows measurements of these variables between the two groups.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Group I</th>
<th>Group II</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Present 35(42.7 %)</td>
<td>20(83.3 %)</td>
<td>15(25.9 %)</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>Absent 47(57.3 %)</td>
<td>4(16.7 %)</td>
<td>43(74.1 %)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Group I: Patients with thrombus; Group II: Patients without thrombus.

Table 1: Patients with atrial fibrillation in both groups (n=82).
DISCUSSION

In this study we evaluated various echocardiographic predictors of thrombus formation. It was observed that significant echocardiographic predictors found in our study. Left atrial thrombus formation is a complication frequently encountered in patients with severe mitral stenosis with a higher chance of systemic embolization leading to higher morbidity and mortality. The increasing severity of mitral stenosis is significantly correlated with increased incidence of thrombus in the left atrium and left atrial appendage. Fifty percent of left atrial thrombi in patients with rheumatic valvular disease, and nearly 90% of left atrial thrombi in patients with non-valvular atrial fibrillation are limited to the LAA. Transesophageal echocardiography is superior to transthoracic echocardiography in the evaluation of LA thrombi. This is confirmed in this study as TEE clearly shows these abnormal changes related to the thrombus formation in the left atrium.

Our study supported that the severity of mitral stenosis was significantly related with thrombus formation as smaller the mitral valve area was. Ozkan et al found similar results. Similarly the frequency of left atrial thrombus increases with atrial fibrillation and low flow velocities. Fazlinez had et al found that patients with left atrial thrombus had more LA appendage dysfunction, more frequent atrial fibrillation and smaller mitral valve area. Our study also supported that atrial fibrillation was significantly associated with thrombus formation (p≤0.05). Ali et al., found similar results in patients of rheumatic mitral stenosis and found that 60% of patients had LA thrombus.

Additionally in our results of low left atrial appendage flow velocities were found to be associated with smaller mitral valve area and larger left atrial size. Guler et al. found that left atrial size was significantly higher in patients with low emptying velocities. In this context, these results are supporting our study as patients with mitral stenosis and low LAA flow velocities
had smaller mitral valve area as compared with those with high LAA blood velocity. We observed more frequent occurrence of left atrial thrombus in patients with atrial fibrillation (83.3%) as compared to sinus rhythm. Goswami et al. found similar results in patients of severe mitral stenosis as they had higher incidence of thrombus formation. In our study atrial fibrillation and left atrial enlargement were significantly associated with thrombus formation. Boonyasirinant et al. found similar results. Golbasi et al. found that left atrial appendage dysfunction leading to thrombus formation can occur in patients of rheumatic mitral stenosis with sinus rhythm. So chances of left atrial thrombus may also be present with sinus rhythm. Conradie et al. found similar results that atrial fibrillation and left atrial enlargement are significant risk factors for thrombus formation in mitral stenosis.

STUDY LIMITATIONS

A smaller number of patients was included in this study and it can lead to variations in results. Also, this is single center experience. Multicenter studies with inclusion of more cases are required. We encountered patients with sinus rhythm and atrial fibrillation together but in future studies both groups should be separately studied.

CONCLUSION

The frequency of left atrial thrombus formation increased in patients with rheumatic mitral stenosis because of low left atrial appendage flow velocities, atrial fibrillation and smaller mitral valve area.

ACKNOWLEDGMENTS

We are extremely thankful to the department of echocardiography Gulab Devi cardiac complex, Lahore and Children hospital and Institute of child health, Lahore. Consent form filled after taking consent from patients. There is no financial support for this study. It was conducted for the partial fulfillment of the degree of B.Sc Hons in Medical Imaging Technology from University of health sciences, Lahore, Pakistan.

CONFLICTS OF INTEREST: No conflict of interest.

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Clinical Trials of Coronary Stents in India: An Update

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ABSTRACT

The Coronary Artery Disease (CAD) burden increased in Indian population and even it is increasing in young Indians. There are more ways to treat these patients and coronary stents are one of the option for them. In the present short communication I am presenting the number of trials, number of patients involved and the limitation of the trials conducted in Indian coronary artery disease patients.

KEYWORDS: Drug eluting stents; Coronary artery disease; National Interventional Council (NIC).

INTRODUCTION

In India the coronary artery disease (CAD) burden increased from last decade and the usage of coronary stents (bare metal and drug eluting Stents) increased. From National Interventional Council (NIC) 2016 data, it is evident that there are more than 4.75 lakhs coronary stents implanted in 2015 year in India and most of them are drug eluting coronary stents. Majority of these coronary stents were imported and having United States Food and Drug Administration (USFDA) approval and CE mark. As per Drugs and Cosmetics Act, stents are notified medical devices and as per Indian FDA rules if the device is having marketing approval and clinical trials in USA or EU, the same device can import to treat Indian patients without conducting any pre-market clinical investigations but need to conduct Post Market Surveillance (PMS) studies in India.

DISCUSSION

At present, there are more than 10 Indian medical devices companies manufacturing drug eluting coronary stents (ex. 3V NEIL from S3V Vascular Technologies Pvt. Ltd.) at affordable price to Indian CAD patients and some of them have CE mark and exporting to other countries.

As per Clinical Trials Registry India (CTRI), hosted at the Indian Council of Medical Research’s (ICMR’s) National Institute of Medical Statistics (NIMS) (http://nims.icmr.nic.in), is a free and online public record system for registration of clinical trials being conducted in India that was launched on July 20th, 2007 (www.ctri.nic.in). Initiated as a voluntary measure, since June 15th, 2009, trial registration in the CTRI has been made mandatory by the Drugs Controller General of India (DCGI).

From CTRI, I found there were 30 coronary stent clinical trials registered to date and a total of 13,934 patients involved in research.

From the registered trials data set, it is evident that:

1. In 29 trials (96.77%) the platform is metal (cobalt chromium or platinum chromium) and in one trial it is Bio-absorbable polymer and it is developed by an indigenous company.

2. The anti-restenotic drugs trend is moved from anti-cancer drugs like paclitaxel to limus...
derivatives and particularly in these Everolimus or Sirolimus dominating the market usage.

3. Only one trial is a proof of concept and rest are either registries or Post Marketing Surveillance (PMS) studies.

4. Most of the trials are initiated by sponsor and very less are investigator initiated and only one trial is a post-graduation thesis.

5. Design wise, most of the trials were single arm and very less are randomized control trials.

6. All the patients were followed-up either clinically or telephonically for at-least 1 year in most of the studies but in some studies, the patients were followed upto 6 years.

7. There are three trials recruited only diabetic patients and involves 25.69% (3580/13934) of total patients involved in all stent trials.

8. Twelve trials are initiated and sponsored by Indian medical device manufacturing companies and involve 1799 patients and it accounts 12.91% of total patients involved in coronary stent clinical trials.

9. Two trials are initiated by investigator and involves 2830 patients and it accounts 20.31% of total patients involved in coronary stent clinical trials.

10. Fifteen trials are initiated and sponsored by multinational medical device manufacturing companies (Foreign companies) and involve 9101 patients and it accounts 65.31% of total patients involved in coronary stent clinical trials.

CONCLUSION

From the Indian coronary stents clinical trials, we can say there is a much need to do more trials in CAD patients and these trials are very less when compared to other countries. The Foreign stent manufacture are conducting more clinical trials than Indian and best part from the trials is, the investigator initiated trials involves a good population and covers more regions of the country. There are more limitations observed in Indian manufacturers initiated trials and the major one is less sample size, so the further trials initiated by Indian manufacturers need to include a good sample size and power. Finally it is very clear that there is no specific guideline from Indian FDA (CDSCO) on PMS of coronary stents, but as per European or USFDA guidelines PMS are mandate and help the nation with the innovative products.

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A Decade of Lipid Profiles: A Gender Focus

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ABSTRACT

Introduction and Objectives: The lipid profile is an important predictor of the risk of coronary heart disease (CHD). Higher rates of total cholesterol (TC) and cholesterol of low-density lipoprotein (LDL-C) increase the chances of developing this disease. However, it is known that women due to hormonal factors would have fewer cardiovascular events. The main objective of this article is to assess the association among different parameters of the lipid profile between the different sexes in the population of a city in Brazil.

Methods: This is a descriptive, longitudinal and retrospective study based on secondary data collected in the period from 2003 to 2013 in a medical laboratory in Aracaju, Brazil. The lipid profile was determined using the following markers: total cholesterol (TC); high-density lipoprotein cholesterol (HDL-C); low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG). Statistical analysis was performed using measures of central tendency and variance. The inferential analysis was performed by student’s t test and the p-value was 0.05.

Results: The sample consists of 63,396 people, 24,425 male and 38,971 female, with mean age of 42.02±17.38 years. The mean value of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride was respectively, 193.39±43.62 mg/dl, 48.80±11.24 mg/dl, 118.35±36.75 mg/dl and 131.28±82.21 mg/dl. Between the genres, it was observed statistical significant differences between all parameters of lipid profile (p<0.0001).

Conclusion: We concluded that women have higher rates of total cholesterol and low-density lipoprotein cholesterol; while men have lower rates of high-density lipoprotein cholesterol and higher of triglyceride, which predisposes males to the development of metabolic syndrome.

KEYWORDS: Dyslipidemia; Epidemiology; Lipid profile; Metabolic syndrome; Genres.

ABBREVIATIONS: CHD: Coronary Heart Disease; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; VLDL: Very low density lipoprotein cholesterol; TG: Triglycerides; TL: Total lipids; CVD: Cardiovascular disease; ANOVA: Analysis of variance; NCEP-ATP III: National Cholesterol Education Program’s-Adult Treatment Panel.

INTRODUCTION

Changes in lifestyle such as alterations in eating habits and the adoption of a sedentary lifestyle, have contributed substantially to the epidemic growing of chronic diseases such as obesity, diabetes mellitus and hypertension, conditions that frequently occurs with lipid abnormalities, hypercoagulability and increased risk of cardiovascular disease (CVD).1,2 A major cause of morbidity and mortality in adults are the atherosclerotic diseases in both developed and developing countries, and dyslipidemia is a primary factor in their emergence.3,4 The onset of the disease can now be detected in childhood, which is considered the
most important period in the prevention of these risk factors.6-8 Keeping this in mind, it becomes necessary to analyze the epidemiological profile for effective prevention and treatment of this disease.

The Brazilian Society of Cardiology (SBC) in 2013, through the V Brazilian guidelines on ‘Dyslipidemia and Prevention of Atherosclerosis’, establishes and recommends monitoring of the lipid profile as a mean of control and prevention of atherosclerosis, using the following parameters: TG, TC, LDL-C and HDL-C.9 Currently, LDL-C above 100 mg/dl appear to be related to increased risk of developing cardiovascular events as well as high levels of triglycerides (above 500 mg/dl) generally predict diseases like acute pancreatitis.8

Data from the Brazilian Ministry of Health in 2009 show that in Aracaju, the capital of the state of Sergipe, the overall prevalence of dyslipidemia in the population is 20.9%, being 18% in men (one of the largest in the country, losing only to Belém, the state capital of Pará) and 23.3% in women. Currently, it is believed that in Aracaju the rates are close to those described previously.10

An analysis by the Brazilian Ministry of Health, in 2010, through a study conducted in nine Brazilian capitals, involving 8,045 subjects (mean age 34.7±9.6 years), showed that serum total cholesterol level was 183±39.8 mg/dl, of which 32.4% of subjects presented levels greater than 200 mg/dl. This amount may represent, in the age group above 50 years, about 19 million Brazilians. Because of this high prevalence of dyslipidemia, it became necessary to stratify patients into different risk groups and develop health policies able to co-opt them for treatment.6

Given the impact of lipid disorders for the health of the general population and in view of the high public spending on treating the consequences of dyslipidemia, such as cardiovascular disease, we intend to trace the lipid profile of the population in the state of Sergipe, Brazil. It is the second study, in this perspective, held in the Northeastern region of our country.

METHODS

This is a descriptive, longitudinal, ecological and retrospective study, based on analysis derived from a secondary database of lipid profiles from a Laboratory of Clinical Analysis of Aracaju, Sergipe, Brazil. Data related to gender and age of the patient, as well as serum levels (in mg/dl) of TC, HDL-C, LDL-C, Very-low-density lipoprotein cholesterol (VLDL-C), TG and total lipids (TL) were collected. The measurement of LDL-C was calculated indirectly through the Friedewald equation11 (LDL-C=TC-HDL-C-TG/5), where TG/S is cholesterol bound to LDL or VLDL-C. The sample was grouped by year, by gender and age in order to enable comparison and statistical analysis of the different variables in this study. According to the V Brazilian dyslipidemia guidelines (SBC 2013), each lipid parameter can be grouped into different categories, namely: good, desirable, borderline, high, very high and low (Tables 1 and 2).9

<table>
<thead>
<tr>
<th>Lipids</th>
<th>Values (mg/dl)</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;200</td>
<td>Desirable</td>
</tr>
<tr>
<td></td>
<td>200-239</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>&gt;240</td>
<td>High</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;100</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>100-129</td>
<td>Desirable</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt;190</td>
<td>Very high</td>
</tr>
<tr>
<td>HDL-C</td>
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<td>Desirable</td>
</tr>
<tr>
<td></td>
<td>&lt;40</td>
<td>Low</td>
</tr>
<tr>
<td>TG</td>
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<td>Desirable</td>
</tr>
<tr>
<td></td>
<td>150-200</td>
<td>Borderline</td>
</tr>
<tr>
<td></td>
<td>200-499</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>Very high</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;130</td>
<td>Good</td>
</tr>
<tr>
<td></td>
<td>130-159</td>
<td>Desirable</td>
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<tr>
<td></td>
<td>160-189</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>&gt;190</td>
<td>Very high</td>
</tr>
</tbody>
</table>

Table 1: Reference values of the lipid profile for adults over 20 years according to the V Brazilian dyslipidemia guidelines (SBC).

<table>
<thead>
<tr>
<th>Lipid Profile</th>
<th>Values (mg/dl)</th>
<th>Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>&lt;150</td>
<td>150-169</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;100</td>
<td>100-129</td>
</tr>
<tr>
<td>HDL-C</td>
<td>&gt;45</td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>&lt;100</td>
<td>100-129</td>
</tr>
</tbody>
</table>

Table 2: Reference values of the lipid profile for children and adolescents (below 20 years) according to the V Brazilian dyslipidemia guidelines (SBC).

In this study, we included the lipid profiles held in the city of Aracaju/SE, from January 2003 to January 2013, in which contained the sex and age of patients. The tests with incomplete data were excluded.

Data were collected from the files of the laboratory on day and time previously scheduled with the technical managers of the institution, with the permission of the coordinator of the Laboratory. The files, available in electronic format, stored on an external HD or USB Pen Drive were transported to laboratory of the Group of Molecular Anatomy, located in the Department of Morphology of the Federal University of Sergipe, Aracaju, Brazil.

The collected data were tabulated in an electronic spreadsheet, making use of Microsoft Excel® (Microsoft Corporation, Redmond, USA, 2007). The inferential analysis was
performed by student’s \( t \) test (two variables) and analysis of variance (ANOVA) (with three or more variables), and results were expressed as mean and standard deviation (SD). It was also analyzed partial correlation between time and variables through the Pearson’s test for statistical analyzes we used the GraphPad Prism 5.0® (GraphPad Software Inc., USA) software and the significance level \((p\text{-value})\) in this study was 0.05.

RESULTS

The sample consisted of 63,396 people, including 24,425 men and 38,971 women with a mean age of 42.02±17.38 years (43.03±17.43 years for women and 40.42±17.18 years for men, \( p<0.0001 \)). The average value of TC, HDL-C, LDL-C, VLDL-C, TG and TL were respectively 193.39±43.62 mg/dl; 48.80±11.24 mg/dl; 118.35±36.75 mg/dl; 26.16±16.46 mg/dl; 131.28±82.21 mg/dl and 565.27±115.88 mg/dl. Between genders, differences were observed for CT (196.59±43.67 mg/dl for women and 188.29±43.06 mg/dl for men, \( p<0.0001 \)), HDL-C (51.21±11.30 mg/dl for women and 44.96±9.99 mg/dl for men, \( p<0.0001 \)), LDL-C (121±37.02 mg/dl for women and 114.11±35.90 mg/dl for men, \( p<0.0001 \)), VLDL-C (24.39±14.24 mg/dl for women and 29.23±19.10 mg/dl for men, \( p<0.0001 \)), TG (121.98±71.18 mg/dl for women and 146.12±95.38 mg/dl for men, \( p<0.0001 \)) and TL (559.05±105.01 mg/dl for women and 575.21±130.75 mg/dl for men, \( p<0.0001 \)) (Figure 1).

In relation to different age groups, we observe the following composition: 7932 persons below 20 years; 21,570 individuals between 21 and 40 years; 24,195 people between 41 and 60 years; 8,944 individuals between 61 and 80 and finally 755 people over 80 years. Comparing the different parameters of lipid profile between the different age groups, we observe statistically significant differences \((p<0.0001)\) in all parameters studied (Figure 2). We also observed weak positive correlations between age and TC values \((r=0.247, p<0.001)\), LDL-C \((r=0.206, p<0.001)\), TG \((r=0.159, p<0.001)\) and TL \((r=0.203, p<0.001)\) in the adult population (20-59 years) and very small negative correlations between age and the different parameters of lipid profile in the elderly, namely TC \((r=-0.075, p<0.001)\), LDL-C \((r=-0.069, p<0.001)\), TG \((r=-0.038, p<0.0015)\) and TL \((r=-0.063, p<0.001)\).

Setting up a time series within the adult age and older, we observed the existence of very small negative correlations between time and all study variables, as follows: CT \((r=-0.04392, p<0.0001)\), LDL-C \((r=-0.02503, p<0.0001)\), HDL-C \((r=-0.009977, p=0.018)\), TC \((r=-0.04984, p<0.0001)\) and LT \((r=-0.06164, p<0.0001)\). It was evident high fluctuation in the average values of these variables over the last 10 years (Figure 3). The same goes for the distribution of lipid parameters between the different sexes (Figures 4 and 5).
Regarding the amount of children and adolescents, two groups were formed: group 1 comprised patients 2-12 years (N=3282) and group 2, 13-20 years (N=4650). The Wilcoxon test showed that there were differences among group means in relation to serum levels of LDL-C, VLDL-C, total cholesterol (TC) and triglycerides (TG), with group 1 always presenting lower values comparing to group 2 (Table 3). In comparison of results with reference values proposed by the V Brazilian guidelines, it was observed that the mean lipid fractions were within the desirable range, with the exception of total cholesterol, which showed a significant discrepancy (alpha=0.05, p<0.0001), reaching the average exceeds 10 mg/dl the optimal value.

DISCUSSION

There are few studies in the literature comparing the lipid profile between different age groups. Some studies have shown direct correlation between increased incidence of cardiovascular disease and total cholesterol levels above 200 mg/dl. In our study, we observed increased levels of this lipid, reaching a peak in the middle age group (41-60 years) and suffering a slight fall in the age group of the elderly. Recent studies show that cholesterol levels of children in a given geographic region would be directly related to the prevalence of coronary artery disease during adulthood in the same region. Because of this, since
2006, the Brazilian Society of Cardiology (SBC) started recommending cut-off for total cholesterol in children and adolescents in 150 mg/dl and routine supervision from 170 mg cholesterol/dl of blood for prevention cardiovascular diseases.13

Studies also show that HDL-C have a protective role in the development of atherogenesis19,20; and the increase of its levels would be directly associated with reduced cardiovascular risk.21,22 In this present study, the behavior was regularly among the different age groups, but was observed between the sexes, significantly higher levels in females, which may explain the lower prevalence of vascular events (CVD and/or stroke) in all ranges age in females compared to males. It is also observed that the presence of high levels of triglycerides associated with low HDL-C, predisposes to the development of acute myocardial infarction during life, in spite of individuals with high levels of triglycerides do not have higher levels of coronary events in relation to population in common.23-25

In the present study, it was observed analogously to total cholesterol, triglycerides higher rates in middle-aged population in comparison to the extreme age (young and elderly); and higher rates in male compared to the female population. These observations, together with the epidemiological characteristics related to HDL-C, mentioned in the previous paragraph, infer a higher prevalence of metabolic syndrome in male middle-aged population, according to the National Cholesterol Education Program’s-Adult Treatment Panel III (NCEP-ATP III), predisposing them to greater prevalence of cardiovascular events (especially myocardial infarction or ischemic stroke).26-28 Now, it is known that the analysis of non-fasting triglycerides could provide important information of remnant lipoproteins (RLPs) associated with increased risk of CHD.9,27

Despite being taken for a long time as a villain, nowadays it is known that LDL-C is not a major risk marker for coronary events currently fitting that role to non-HDL cholesterol (which includes the fractions of very low molecular weight-VLDL), especially in cases of hypertriglyceridemia associated with diabetes, metabolic syndrome or renal chronic disease.30,31 However, the most recent consensus is still maintained LDL cholesterol as the primary target for therapy, especially in those patients with triglyceride levels below 200 mg/dl, because at these levels, the ratio between LDL cholesterol and HDL-C is no next.32,33 These findings were in agreement with our study, which was detected higher rates of LDL-C in females compared to males.

Regarding the historical evolution of the different lipid parameters through 10 years, there has been a slight reduction in all the parameters. This indicates that those factors associated with the onset of dyslipidemia, such as a diet rich in fatty foods and little physical exercises are still present in our population.10,31 Therefore, public policies are needed to change health habits, reducing the probability of occurrence of cardiovascular diseases.32,33

CONCLUSION

We hope that this research contributes to the knowledge of the prevalence of lipid abnormalities in our state and can be used to prevention and control of dyslipidemia in Sergipe and, by extension, in Brazil.30,34

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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27. Frost PH, Havel RJ. Rationale for use of non-high density


Primary Angioplasty Using a Renal Stent in a Severly Ectactic and Occluded Left Anterior Descending Coronary Artery

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ABSTRACT
Revascularization of ectatic coronary arteries in the setting of acute myocardial infarction poses great challenges for the operator. We report a case, where a peripheral renal stent was used successfully to treat the clinical situation.

KEYWORDS: Renal stent; Coronary artery ectasia; Primary angioplasty.

INTRODUCTION
Coronary artery ectasia (CAE) is defined as dilatation of an arterial segment to a diameter at least 1.5 times that of the adjacent normal coronary artery.1 It is found to occur in 1.2-4.7% of patients undergoing coronary angiography (CAG).2 The etiologies of CAE are atherosclerosis in 50% cases, congenital in 20-30% while 10-20% are associated with connective tissue disorders.3

CAE is not a benign entity as it leads to sluggish or turbulent coronary blood flow, with exercise induced angina and myocardial infarction (MI), regardless of the severity of co-existing stenotic coronary disease, arrhythmia and sudden cardiac death. This is due to repeated dissemination of microthrombi to segments distal to the ectasia, or to thrombotic occlusion of the dilated vessel. Slow flow during a procedure or spontaneously may also be a causative factor.3

Acute coronary syndromes such as MI in the setting of underlying CAE pose serious therapeutic challenges for the operator because 1) No clear-cut guidelines exist regarding what treatment strategy is to be used (fibrinolysis, balloon angioplasty or stenting). 2) Dedicated hardware especially large diameter coronary stents required for such cases are not available and 3) High thrombus burden poses significant challenges.

We recently encountered one such case where a patient presented with acute ST elevation MI and had severe CAE which was successfully treated using a renal stenting, there being no coronary stent more than 5 mm being manufactured.

CASE SERIES
A fifty-six-year-old hypertensive male presented to the Emergency Department with severe retrosternal discomfort of 2 hours duration. An urgent electrocardiogram (ECG) was suggestive of acute anterior wall MI. His heart rate was 72 per minute; blood pressure 130/80 mmHg. Cardiovascular and respiratory system examination were unremarkable. He received a loading dose of 180 mg ticagrelor, 325 mg as aspirin and 80 mg of atorvastatin. After an informed

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consent was obtained a coronary angiogram was immediately performed which revealed severe CEA. The right coronary artery (RCA) and left circumflex (LCx) were ectatic but had no obstructive lesions; however the left anterior descending artery apart from being ectatic (approximately 7 mm in diameter) was 100% occluded proximally (Figure 1A and 1B). The technical challenges posed by these angiographic findings were discussed with the patient and his relatives and the options of either fibrinolytic therapy or percutaneous coronary intervention (PCI) and implantation of a peripheral stent in the left anterior descending artery (LAD) were offered. They opted for the latter treatment option after all pros and cons were explained. The left coronary ostium was engaged using a Judkins left (JL 4) 7F guiding catheter. The lesion was crossed using an All star 0.014”×180 cms percutaneous transluminal coronary angioplasty (PTCA) wire (Abbot Vascular, Santa Clara, CA, USA) and significant thrombus burden was noted in the LAD (Figure 2A). Injection Abciximab bolus and infusion was initiated as per protocol. Repeated thrombus aspiration was carried out using a Thrombuster II catheter (Kaneka Corporation, Osaka, Japan) and thrombotic material was retrieved. Subsequently once reasonably satisfactory flow was achieved in the LAD and the culprit lesion identified (Figure 2B) it was stented using a 7×18 mm RX Herculink Elite Renal Stent (Abbot Vascular, Santa Clara, CA, USA) deployed at 11 atmospheres (Figure 2C). The stent system has a shaft length of 135 cms. Thrombolysis in Myocardial Infarction (TIMI) III flow was achieved in the vessel (Figure 2D) with resolution of symptoms. Post PCI period was uneventful and patient was discharged successfully on dual antiplatelet therapy (Aspirin and Ticagrelor), statins, beta blocker and Angiotensin
converting enzyme inhibitor. The patient is doing well 4 weeks after the procedure.

DISCUSSION

CAE poses significant management challenges. Various medical treatments tried include empiric chronic anticoagulation, dual antiplatelet therapy and medications with vasodilatory properties (nitrates, calcium channel blockers, angiotensin-converting-enzyme inhibitor (ACE) inhibitors and trimetazidine). However no prospective studies have been carried out and these cannot be recommended at present as a standard of care. Nitrates theoretically seem to be appropriate in patients with CAE due to their ability to cause coronary dilatation, however on the contrary they have been shown to exacerbate myocardial ischemia. Stent implantation is recommended only when significant stenosis accompanies the CAE and medical therapy has not been successful. This is because these lesions have heterogeneous morphologies, large caliber making it difficult to determine stent type, size and complete expansion. If the target lesion is not suitable for stent implantation, surgical excision or ligation with a bypass graft could be choice of treatment.

However a real dilemma is when one is faced with a CAE in an acute MI situation as in the present patient. The treatment options include fibrinolysis, plain balloon angioplasty or stenting with a peripheral stent. Oh et al described two cases of ACS in CAE setting. One patient underwent plain balloon angioplasty while the other received a 6×24 mm Genesis peripheral stent. Agarbasli et al reported 3 cases of coronary angioplasty with intra-therapeutic peripheral biliary stents for CAE. This was the first report of using a peripheral biliary stent for coronary revascularization. Rha et al reported the use of two parallel stents (3.5×18 mm sirolimus eluting stents) in a patient with CAE. In the present case the vessel diameter was 7 mm and the renal stent available on shelf had the desired dimensions and also a shaft length of 135 cms such that it could be delivered to the desired site in the coronary tree. As far as options of Antiplatelet therapy are concerned usually after placing peripheral stents dual antiplatelet therapy (DAPT) is continued and is stopped. In this case as a peripheral stent was used in coronary location we plan to continue DAPT for 1 year and then switch over to single Antiplatelet drug in accordance with ACC/AHA guidelines for coronary stents. To the best of our knowledge this is the first case in literature where a renal stent has been used in the coronary tree.

CONCLUSION

Surprises may spring up at any given time in the cardiac catheterization laboratory. Unusual scenarios such the one mentioned above may call for quick and out of the box thinking. Peripheral stents may help revascularize ectatic vessels in which routinely available coronary stents cannot be used due to sizing constraints.

Industry in collaboration with interventional cardiologists needs to develop hardware for PCI of vessels with ectasia. In view of the mismatches in the size of these vessels a self-expanding stent seems the most appropriate.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

Diagnostic Value of Coronary CT Angiography With Use of Left Coronary Bifurcation Angle in Coronary Artery Disease 

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ABSTRACT

Background: Atherosclerosis generally occurs in the blood vessels with angulation or curvature, however, association between coronary bifurcation angle and coronary artery disease needs to be further clarified when compared to normal patients.

Objectives: The aim of this study is to determine the relationship between left coronary bifurcation angle and development of coronary artery disease when compared to patients with normal coronary arteries.

Methods: Fifty patients (40 men, mean age, 55.2 years) who underwent coronary computed tomography (CT) angiography for clinical diagnosis of coronary artery disease were included in the study. Of these patients, coronary plaques were present at one or more coronary arteries in 25 patients, while in the remaining 25 cases, no plaque was detected at the coronary arteries, thus serving as the control group. Left coronary bifurcation angle between left anterior descending and left circumflex was measured on 3D volume rendering images by two assessors with >80º as the cut-off value to determine significant stenosis.

Results: The mean bifurcation angle was 72.9º±19.4º (range, 36º, 112º) among 50 patients. The mean bifurcation angle was significantly wider in patients with coronary plaques than that measured in patients with normal coronary artery (p<0.001), with corresponding values being 83.9º±17.5º (range, 45º,112º) and 62.5º±15.4º (range, 36º, 89º). Of 25 patients with coronary plaques, 18 (72%) had a bifurcation angle >80º, while only 12% of the patients had a bifurcation angle >80º in the control group.

Conclusion: This study further confirms the direct relationship between left coronary bifurcation angle and development of coronary artery disease with diseased coronary arteries associated with wider angulation.

KEYWORDS: Bifurcation angle; Coronary artery disease; Coronary CT angiography; Coronary plaque; Measurement.


INTRODUCTION

Coronary computed tomography angiography (CCTA) has been widely accepted as a less-invasive imaging modality with high diagnostic value in the diagnosis of coronary artery disease due to rapid technological developments in multislice CT scanners. While radiation dose associated with CCTA has been significantly reduced with use of various dose-reduction strat-
egies, the limitations of CCTA lie in two aspects: inferior temporal resolution and effect of heavily calcified plaques on the reliable detection of coronary stenosis. The temporal resolution of current multislice CT scanners is between 83 and 175 ms, thus, use of beta-blockers is necessary to control heart rate in most of the patients with heart rate >70 beats per minute, although high diagnostic value of CCTA in patients with high heart rates has been reported in some recent studies using latest CT scanners.6-10 It is well known that high calcification or high calcium score in the coronary arteries results in false positive results, thus leading to low specificity and positive predictive value (PPV).11-15 This limitation has been addressed to some extent with use of image processing methods as reported in some studies.16-18

Another approach to improve diagnostic value of CCTA in the diagnosis of calcified plaques is to use left coronary bifurcation angle as opposed to the conventional method of measuring coronary lumen stenosis. Recent studies have shown that diagnostic accuracy of CCTA has been significantly augmented with use of bifurcation angle as a criterion to determine coronary stenosis when compared to assessment of the degree of lumen stenosis.16-21 Despite these promising results, it is still necessary to clarify the role of bifurcation angle in both normal and diseased coronary arteries. Thus, the purpose of this study is to further clarify the clinical value of CCTA with use of left coronary bifurcation angle in the diagnosis of coronary artery disease. We hypothesized that wider angulation is associated with higher prevalence of coronary plaques when compared to the normal coronary arteries.

METHODS

Study Population

This retrospective study involves reviewing consecutive patients who underwent CCTA examination for diagnostic assessment of coronary artery disease. Eligible criteria included successful completion of CCTA scans with good image quality for demonstration of coronary arteries. Patients were excluded if they had known allergy to contrast medium, prior history of coronary stenting or coronary artery bypass surgery, impaired renal function or unable to control heart rate less than 65 beats per minute after beta-blockers were administered. Fifty-one patients met our selection criteria and were included in the analysis. In all examinations, non-ionic contrast medium Ultravist 370 mg/ml (Ultravist 370, Bayer Schering Pharma AG, Taipei, Taiwan) was delivered using a dual-head power injector. The scan was initiated with use of bolus tracking technique with a CT attenuation of 120 HU as the triggering threshold in the ascending aorta. Forty-five to 55 ml contrast medium was injected at an injection rate of 3.0 ml/s followed by a saline flush of 30-40 ml. Pitch ranged from 0.2-0.4. Images were reconstructed with a slice thickness of 0.6-0.625 mm and a reconstruction interval of 0.3-0.33 mm resulting in the voxel size ranging from 0.30x0.30x0.30 mm³ to 0.33x0.33x0.33 mm³.

Image Analysis and Measurement of Bifurcation Angle

CCTA images in digital imaging and communications in medicine (DICOM) format were transferred to a separate workstation equipped with Analyze V 12.0 software (AnalyzeDirect, Inc., Lexana, KS, USA) for image post-processing and analysis. Analyze is a biomedical software enabling robust analysis of medical images including various views consisting of 2D and 3D reconstructed images and 3D virtual intravascular endoscopic visualizations.21-23

Left main bifurcation angle between left anterior descending (LAD) and left circumflex (LCx) was measured to determine the correlation between bifurcation angle and coronary plaques. Three-dimensional (3D) volume rendering (VR) images reconstructed from 2D axial CCTA were used to measure the bifurcation angle between LAD and LCx (Figure 1). Measurements were performed by two assessors independently. Three consecutive measurements of the bifurcation angle were obtained in each case with the mean value taken as final to minimize biased results. In addition to the bifurcation angle measurement, assessors analyzed the coronary plaque characteristics in terms of plaque composition, such as calcified, non-calcified or mixed plaques, as well as plaque distribution in the coronary arteries. The inter-observer agreement and intra-observer agreement was good with 95% and 91%, respectively. A degree of >80° bifurcation angle is used as a cut-off value to determine significant coronary artery disease or stenosis, according to pre-

Ethical approval from Institutional Review Board (IRB) was waived in this study since CCTA image acquisition was part of the clinical referral for diagnosis of coronary artery disease. Due to retrospective nature of this study, there is no need for obtaining informed consent from the patients.

CCTA Scanning Protocols

All patients were scanned in the second generation dual-source 128-slice CT (Siemens Definition Flash, Siemens Healthcare, Forchheim, Germany) and 256-slice CT scanners (Brilliance iCT, Philips Healthcare, Cleveland, OH, USA), with the following imaging protocols: detector collimation 2×64×0.6 mm, gantry rotation of 0.28 s, with a tube voltage of 120 kVp for Siemens scanner, and 2×128×0.625 mm with a dynamic z-focal spot, gantry rotation of 0.27 s, with a tube voltage of 120 kVp for Philips iCT, respectively. All scans were performed with retrospective ECG gating with images targeting a diastolic phase at 75% of R-R interval. Beta-blockers were administered in patients with heart rate >65 beats per minute prior to the CT scans. In all examinations, non-ionic contrast medium Ultravist 370 mg/ml (Ultravist 370, Bayer Schering Pharma AG, Taipei, Taiwan) was delivered using a dual-head power injector. The scan was initiated with use of bolus tracking technique with a CT attenuation of 120 HU as the triggering threshold in the ascending aorta. Forty-five to 55 ml contrast medium was injected at an injection rate of 3.0 ml/s followed by a saline flush of 30-40 ml. Pitch ranged from 0.2-0.4. Images were reconstructed with a slice thickness of 0.6-0.625 mm and a reconstruction interval of 0.3-0.33 mm resulting in the voxel size ranging from 0.30x0.30x0.30 mm³ to 0.33x0.33x0.33 mm³.
previous studies.18-21

Statistical Analysis

Statistical analysis were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA). Continuous variables were expressed as mean±standard deviation, while categorical variables were presented as percentages. Chi-square test was used for categorical variables between the two groups (or Fisher’s Exact test was used if the variable or an event was observed in less than 5 cases). Comparison was performed using one sample t-test. A p value of <.05 was considered statistically significant.

RESULTS

CCTA was successfully performed in all patients with no complications. Of 50 cases, image quality was found good or excellent in 48 cases with the mean CT attenuation more than 300 HU (Hounsfield unit) or signal-to-noise ratio (SNR) more than 10 in the ascending aorta or coronary artery. In the remaining 2 cases, CT attenuation was lower than 160 HU in one case, and high standard deviation in another case resulting in low SNR (7.8). Table 1 shows patient’s characteristics and plaque distribution in the coronary arteries.

The mean bifurcation angle was measured 72.9º±19.4º (range, 36°,112°) among all 50 patients (25 in the group with normal coronary artery and 25 in the group with coronary plaques). The mean bifurcation angle in patients with coronary plaques was measured 83.9º±17.5º (range, 45°,112°), and this is significantly wider than that measured in patients with the normal coronary artery, which was 62.5º±15.4º (range, 36°,89°) (p<0.001) (Table 1). Of 25 patients with coronary plaques, 18 (72%) had a bifurcation angle >80º, while in contrast, only 12% of the patients had a bifurcation angle >80º in the control group. Of 25 cases with coronary plaques, most of them were found to be calcified (84%), while mixed plaques were noted in 4 cases.

Table 1: Patient characteristics and plaque distribution.

<table>
<thead>
<tr>
<th>Parameters for comparison</th>
<th>Study group (25)</th>
<th>Control group (25)</th>
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<tbody>
<tr>
<td>Mean age±SD*</td>
<td>58.3±6.0</td>
<td>52.2±9.4</td>
</tr>
<tr>
<td>Mean angle±SD*</td>
<td>83.9±17.1</td>
<td>62.5±15.4</td>
</tr>
<tr>
<td>Gender: M:F</td>
<td>22:3</td>
<td>18:7</td>
</tr>
<tr>
<td>Plaque distribution (%)</td>
<td>LAD: 44%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>LCx: 4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RCA: 4%</td>
<td></td>
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<tr>
<td></td>
<td>2-vessel disease: 24%</td>
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<tr>
<td></td>
<td>3-vessel disease: 24%</td>
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<tr>
<td>No. of cases in relation to age group (years)</td>
<td>41-50: 8%</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>51-60: 64%</td>
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<tr>
<td></td>
<td>61-70: 24%</td>
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<tr>
<td></td>
<td>71-80: 4%</td>
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</tbody>
</table>

LAD-left anterior descending, LCx-left circumflex, RCA-right coronary artery, N/A-not applicable, SD-standard deviation.

*p indicates significant difference (p<0.05).
DISCUSSION

This study further clarifies the accuracy of using left coronary bifurcation angle to determine coronary artery disease. Results of this study showed that patients with coronary artery plaques are associated with wider angulation, while narrower angulation is seen in patients with normal coronary arteries. Therefore, based on current available literature, while waiting for additional large studies evaluating the prognostic role of this parameter, the analysis of bifurcation angle measurement, especially for left main, may be considered during the routine diagnostic assessment of coronary artery disease.

The rationale of measuring coronary bifurcation angle is because of the relationship between hemodynamic changes and atherosclerotic development at bifurcation regions. Both clinical studies and hemodynamic analysis using computer modelling have shown that plaques usually occur in the vascular areas with angulation or abrupt curvatures.24-29 Our early report showed a direct correlation between left coronary bifurcation angle and coronary diameter changes with significantly wider angle and larger diameter in diseased coronary arteries when...
compared to the normal ones. This has been confirmed by a recent study investigating the association between bifurcation angle and risk factors of developing coronary artery disease. Based on analysis of 196 patients with suspected coronary artery disease, Temov and Sun concluded that male patients and patients with large body mass index were more than 2-fold likely to have wider angulation (>80°) with associated higher risk of coronary artery disease. This study further highlights the additional value of using bifurcation angle for diagnosis of coronary artery disease through a direct comparison between diseased patients and the normal ones.

Using bifurcation angle as a diagnostic parameter has also been shown to improve the diagnostic value of CCTA in the detection of calcified plaques. Low diagnostic specificity and PPV of CCTA in calcified plaques is mainly due to high false positive rates caused by blooming artifacts which result from heavy calcification in the coronary arteries. This is a widely known limitation of CCTA. Some recent studies have addressed this issue by showing the improved diagnostic performance of CCTA with use of bifurcation angle measurement when compared to the conventional approach based on coronary lumen stenosis. The specificity and PPV were improved from 33% and 43% to 79% and 81%, corresponding to CCTA by coronary lumen diameter and bifurcation angle measurements, respectively. Although diagnostic value of CCTA was not assessed in this study due to inclusion of low to intermediate pretest probability of coronary artery disease without having invasive coronary angiography as the reference standard, findings are consistent with these previous reports showing the improved accuracy of CCTA using bifurcation angle.

Although this is a retrospective study based on a small number of cases, results through a direct comparison between two groups add valuable information to the existing studies. Findings of this study further strengthen the previous reports that left coronary bifurcation angle is a more accurate method for determining significant coronary stenosis than coronary lumen assessment. However, some limitations in this study should be acknowledged. First, a small sample size is one of the main limitations. Inclusion of more patients, especially with more clinical centers’ involvement would be desirable to allow us to draw robust conclusions. Second, as discussed above, there is no correlation of CCTA findings with invasive coronary angiography, therefore, no diagnostic value is available. Further, due to the retrospective nature, risk factors associated with coronary artery disease are not available in most of the patients in this study. However, the association between common risk factors and coronary artery disease has been well studied in a recently published study. Finally, although plaque distribution and type of plaque were analyzed, due to limited number of cases, there is no analysis of plaque features, in particular, analysis of plaque composition such as low-attenuating plaque, plaque volume and length which are commonly used to indicate the plaque vulnerability. Thus, further studies should focus on the analysis of these features in relation to their association with bifurcation angle measurement.

In conclusion, this study further confirms the relationship between left coronary bifurcation angle and coronary artery disease with diseased coronary artery associated with wider angulation when compared to the normal coronary arteries. Further research is required to investigate the plaque composition in relation to the bifurcation angle with the aim of identifying high-risk plaque or plaque vulnerability, preferably to be conducted at multicenter sites with inclusion of more patients.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES


29. Pang CL, Alcock R, Pilkington N, Reis T, Roobottom C.

