Predicting and Optimizing Response to Cardiac Resynchronization Therapy Beyond QRS Duration: Expanding Role of Echocardiography

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Although many medical therapies are currently available for advanced cardiac dysfunction, there are fewer non-medical options. One of these options, Cardiac Resynchronization Therapy (CRT), targets the aberrant pattern of ventricular activation thereby reducing intra and interventricular asynchrony. Currently, heart failure patients with New York Heart Association class III or IV symptoms, a QRS duration greater than > 120 milliseconds (ms), and an ejection fraction (EF) ≤ 35% qualify for cardiac resynchronization. However, up to 30% of patients are deemed "nonresponders" with little to no improvement in symptoms, exercise capacity, or left ventricular (LV) function.[1] This large number of nonresponders has led to novel approaches to CRT including the identification of more precise predictors of response, a broader patient population with asynchrony and newer approaches to biventricular cardiac pacing.

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Various echocardiographic measures of ventricular asynchrony beyond just ejection fraction and a widened QRS have been investigated in the hope of prognosticating response to CRT. These attempts at a more precise mechanical predictor of response have only been validated in small numbers of patients. The difference between left and right ventricular pre-ejection intervals (time of onset of QRS to beginning of aortic Doppler VTI subtracted from time of onset of QRS to beginning of pulmonic Doppler VTI) is a straightforward and readily available assessment of interventricular dyssynchrony. In CARE-HF patients with an interventricular delay of ≥ 49.2 milliseconds, cardiac resynchronization reduced the LV volume index, the area of the mitral regurgitant jet, increased the LVEF and improved symptoms and quality of life.[2]

M-mode echocardiography has been shown to predict which patients will benefit from resynchronization therapy. During a follow-up of 14 months in 60 patients, a delay between maximal septal wall displacement to maximal posterior wall displacement ≥ 130 milliseconds accurately predicted a significant increase in EF compared to a delay < 130 milliseconds. This was also correlated with a significant increase in event free survival and reverse remodeling compared to QRS duration alone (65%).[3, 4]

With the most published data of all echocardiographic parameters, Tissue Doppler Imaging (TDI) has shown the greatest promise in predicting resynchronization response. TDI allows for the determination of regional time to peak systolic velocity (S wave) while Tissue Synchronization Imaging (TSI) allows the quantitative determination of regional orthogonal wall delays by color coding time to local peak velocities. Bax and colleagues originally demonstrated that a septal to lateral delay of ≥ 65 milliseconds (Figure 1) was able to identify responders with a sensitivity and specificity of 80% to predict clinical improvement and 92% to predict LV reverse remodeling. More dramatically, those patients with a ≥ 65 milliseconds dyssynchrony had a 6% event rate compared to those patients with less than 65 milliseconds dyssynchrony after CRT (follow-up 6 months).[5,6]

Strain and strain rate are both variations using Tissue Doppler Imaging. In practice, measured parameters include the time to peak myocardial strain, the time to peak strain rate and time to peak regional systolic velocity. Yu and colleagues found the standard deviation of a 12 segment left ventricular model as the most powerful predictor of reverse remodeling by measure of LV end-systolic volume reduction after biventricular pacing.[7–9] Other models involving echocardiographic phase analysis, radial dyssynchrony, velocity vector imaging and delayed longitudinal contraction have all been validated.[10–13]

Three dimensional echocardiography (3D echo) represents the most recent technique for evaluating ventricular

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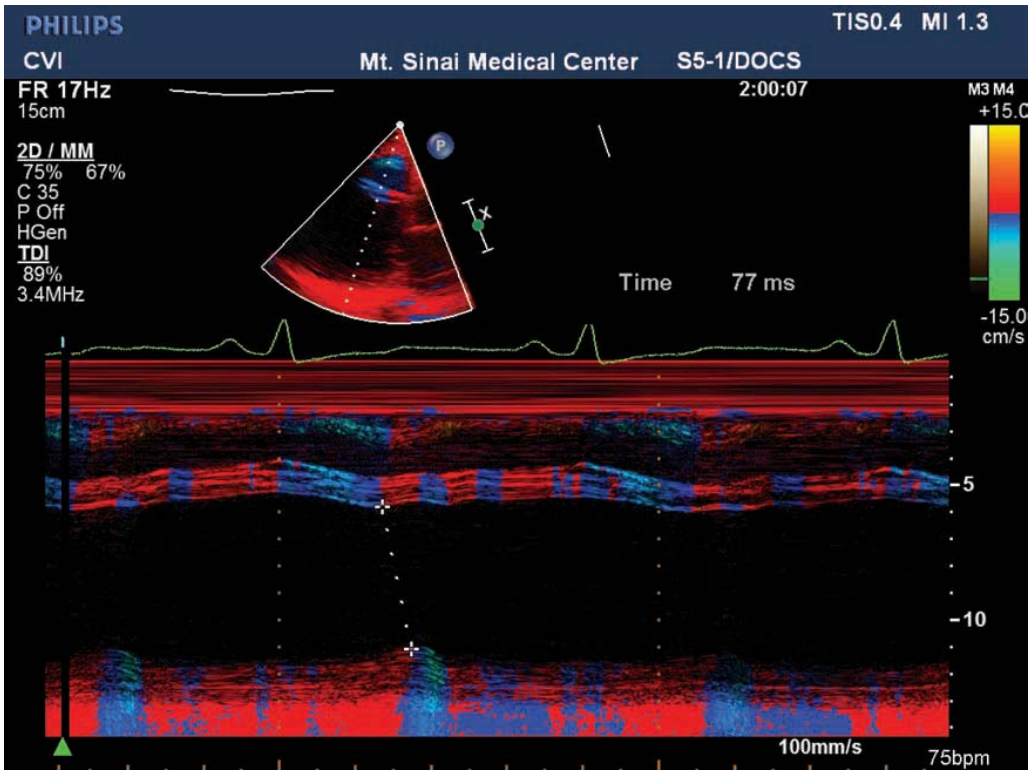

Figure 1. Septal to lateral delay (77 ms) using TDI. A cutoff of > 65 ms is predictive of favorable response to cardiac resynchronization.

dyssynchrony. The simultaneous acquisition of the entire left ventricle may overcome some of the limitations of other techniques which sample only small portions of the ventricle often on different cardiac cycles.[14] Splitting the left ventricle into 16 segments (Figure 2), Kapetanakis *et al* derived a Systolic Dyssynchrony Index (SDI) based on the time to minimal regional volume. Responders demonstrated significant reduction in SDI and end-diastolic volume at ten months.[15] However, to date, there are no studies using 3D dyssynchrony parameters to predict who will respond to cardiac resynchronization therapy.

While these echocardiographic measurements are mechanical surrogates for ventricular asynchrony, QRS duration and ejection fraction are the current surrogate markers for ventricular asynchrony that are used to differentiate responders from nonresponders in the current CRT guidelines. However, numerous studies have shown that patients with a QRS duration ≤ 120 milliseconds have dyssynchrony as well. Perry and colleagues screened 100 patients with an EF ≤ 35% regardless of QRS duration using TSI. Of this cohort, 65% of those patients with dyssynchrony (31 patients) had a narrow QRS.[16] The RAVE investigators studied 193 patients with EF < 40% and narrow QRS using multiple methods (pre-ejection intervals, TDI, M-mode) and found that depending on whichever method was used, patients exhibited dyssynchrony anywhere between 21% to 73%.[17] This corresponds to other estimates of ventricular systolic asynchrony prevalence ranging anywhere between 27 to 51% in similar patient populations.[15, 18, 19]

CRT appears to be beneficial in these patients based on the results of preliminary studies. Bleeker and colleagues implanted biventricular pacemakers in 33 patients with an EF ≤ 35% along with narrow complex QRS duration (< 120 milliseconds) and compared functional class and LV end-systolic volume to a group of similar patients with prolonged QRS. There was no statistical difference in either measured parameter at 6 months between the two groups. All patients met TDI criteria for dyssynchrony prior to enrollment.[20] Achilli *et al* demonstrated similar benefits in 14 patients when compared to a classic patient population with wide QRS.[21] Studies are ongoing, with enrollment in RETHINQ completed, data from this study will help answer the question of benefit of resynchronization in narrow QRS patients.

Kumar and Goel, in this issue of IHJ,[22] evaluated the presence of ventricular asynchrony in patients with dilated cardiomyopathy and various QRS widths. Additionally, they sought to determine a correlation, if any, of severity of left ventricular dysfunction and the occurrence of ventricular

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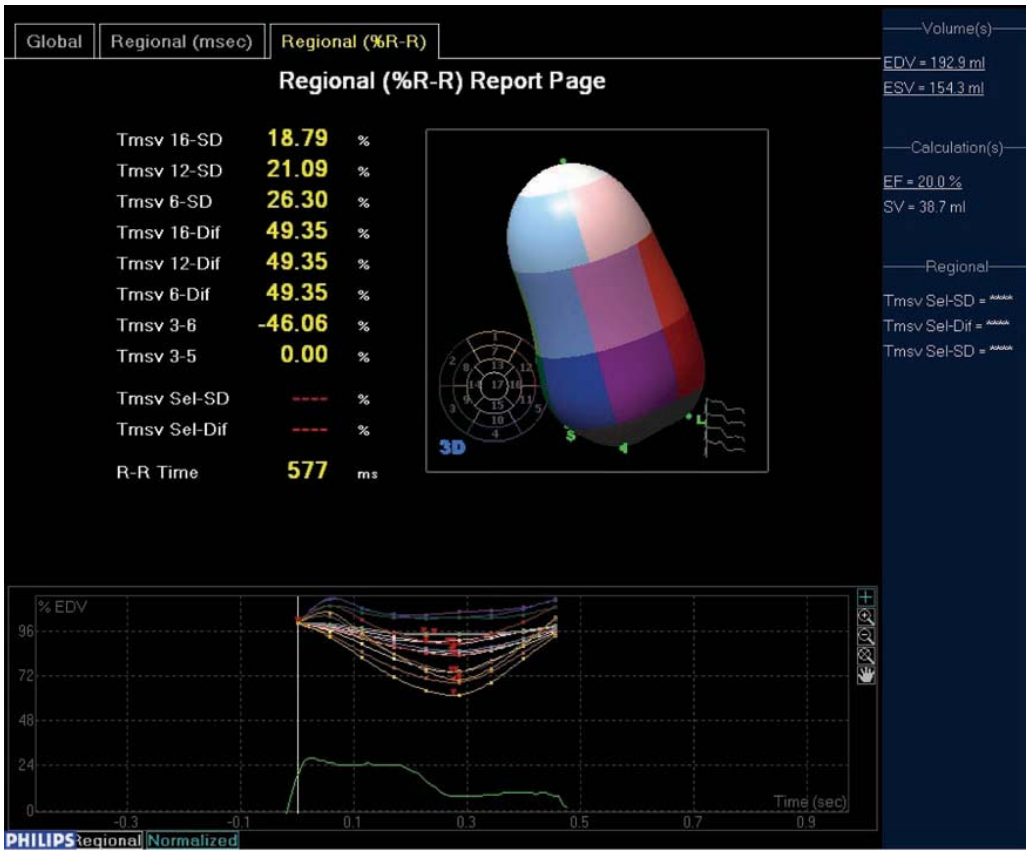

Figure 2. 16 segment systolic dyssynchrony index using three-dimensional echocardiography

dyssynchrony. Results were most striking in the group with EF $<$ 40% and QRS $\leq$ 120 milliseconds. Ventricular asynchrony was found in nearly 51% of these patients. Those patients with an EF of $<$ 20% and QRS $>$ 120 milliseconds had an astonishingly high 97.5% interventricular asynchrony rate, but any conclusive correlation between left ventricular function and ventricular dyssynchrony was not found. While it is not surprising that a fair number of subjects had dyssynchrony despite a "narrow" QRS, given the findings of previously published studies, these results serve to underscore the fact that QRS duration and EF are only surrogates for ventricular asynchrony and there may be a larger population of patients that may benefit from CRT. However, not all types of echocardiographic dyssynchrony have been shown to be predictive of resynchronization and a comparison of multiple echocardiographic dyssynchrony measurements, especially TDI, would be helpful in predicting who might respond best to cardiac resynchronization.

As the eligible patient population for CRT will most certainly increase in the future with the addition of narrow QRS patients and other novel cohorts, contemporary studies are now looking at diverse pacing techniques for patients with advanced heart failure. One of these techniques, LV pacing, is garnering more attention.[23] Most recently, Rao and colleagues performed a head to head comparison between simultaneous biventricular, sequential biventricular and LV pacing. At 3 and 6 months, the simultaneous biventricular pacing group exhibited a trend towards greater improvement in LV size while all groups had a significant improvement in stroke volume and LVEF.[24]

Further, Dwivedi *et al* in this issue of the Journal,[25] help determine the acute hemodynamic impact of biventricular pacing compared with isolated left ventricular pacing in patients with left ventricular dysfunction and QRS $\leq$ 120 milliseconds. As a group, biventricular pacing raised blood pressure, pulse pressure, left ventricular EF, cardiac output and left ventricular dP/dT from baseline. However, the protocol had limitations including no long term follow-up, small numbers of patients, no pre-pacing determinants of echocardiographic dyssynchrony and medical non-optimization. Even though, the observations fill a void of knowledge in the area of pacing hemodynamics, further studies are needed to confirm the positive findings seen in the paper and elucidate their mechanisms.

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With the recognized high number of non-responders, more research attention is now focused on pre-implantation predictors of response, prevalence of dyssynchrony in non-classic patients and the understanding of pacing hemodynamics. New frontiers in CRT (quantification of electrical and mechanical dyssynchrony, CRT optimization, lead placement, contribution of scar, etc.) need to be explored for further refinement of biventricular pacing qualification and resynchronization technique.

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Coronary Artery Calcium and You—Do You Know Where You Stand?

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For nearly two decades we have been utilizing computed tomography (CT) to estimate the extent of coronary artery calcification first by electron-beam CT and then more recently by multidetector row computed tomography (MDCT).

The universal Agatston method of calculating coronary artery calcium (CAC) is now etched into the memory of CT acquisition workstations, and therefore it seems into the minds of many young doctors as an important tool for estimating coronary plaque burden and assessing cardiovascular risk.[1] But this has not always been the case. In fact as recently as year 2000, the ACC/AHA Expert Committee Document concluded that there was insufficient evidence for using CAC measurement to predict coronary heart disease events and cardiovascular risk.[2] Yet even at that time, great strides had already been taken to better understand the potential of this new technology and of the relationship between coronary artery calcification with atherosclerosis, plaque rupture and progression. For example, we know atherosclerotic plaque instability can lead to rupture and acute thrombosis and that the healing of these ruptured lesions are associated with spotty calcification on CT, an observation that is also noted on intravascular ultrasound. The unstable plaque which represents an early stage of atherosclerosis development is probably non-calcified.[3] On the other hand extensive calcification is usually associated with fairly advanced and presumably stable plaques.[4] Therefore it appears that heavy calcification and high CAC sore should not necessarily increase risk of coronary events. No–argue the experts. Patients who have calcified plaques are also more likely to harbor non-calcified plaques which are more vulnerable to rupture. It is the co-existence of both calcified and non-calcified plaques that provide the means for estimating acute coronary events.[2,4]

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And they're right–as vindicated by recent large cohort studies, meta-analyses and systemic reviews. In the latest ACCF/AHA Expert Consensus Document of CAC led by Philip Greenland and jointly developed with the Society of Atherosclerosis Imaging and Society of Cardiovascular Computed Tomography,[5] the results of these studies that included over 30,000 asymptomatic patients were considered.[6–11] Patients without detectable calcium (CAC Score of 0 by Agaston Method) have a very low rate of myocardial infarction (MI) or cardiovascular-related death –0.4% over 3 to 5 years. In comparison, patients with any detectable calcium have a 4-fold increase in risk of coronary events. There was incremental relationship where higher CAC scores are associated with higher event rates. So for patients whose CAC Score fall within 1–100, 101–400, 401–1000 and 1000 and above, the relative risk ratios when compared to CAC Score of 0 are 1.9, 4.3, 7.2 and 10.8 respectively. So we finally have evidence and expert consensus that CAC score is a reliable tool for estimating coronary events and cardiovascular risk.

Next we need to put CAC scoring by CT into perspective and judge it according to current established practice and methods for estimating risk. Several scoring systems exist globally, the most popular being the Framingham Risk Score (FRS) model and the PROCAM model developed based upon the German Munster Study.[12] The components of these methods take into account age, gender, lipid

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profiles, presence of diabetes, hypertension and exposure to nicotine smoking. Several observational cohort studies have demonstrated that CAC Score provided additional independent risk predictive value over and above these models, and even after inclusion of novel risk markers such as hs-CRP.[6–11] But the risk conferred did not further alter the patient's overall risk status (categories of low, intermediate, high or very-high risk) except in the intermediate-risk group. If a patient's CAC Score was 400 and above, then the additional risk of 2.4% per year pushes this patient into the high risk category at need of intensive medical therapy. So here is the second important point; that CAC scoring is useful in the asymptomatic patient of intermediate-cardiovascular risk equivalent to 10–20% over 10 years, but not for the low-risk patient nor for the high risk patient in whom additional knowledge of CAC score would not alter clinical management and decision.

What additional value does the article by Dr Wasnick add to the current literature on CAC scoring?[13] Plenty. For a start, the majority of world literature on this subject have tended to focus on primarily male Caucasian populations and patients. Very few have looked at the Asian Indian population, who are arguably at higher risk of everything–dyslipidemia, central obesity, diabetes, insulin resistance, cardiovascular events and deaths–compared to other Asian ethnic groups. Hence the paper provides a pioneer effort to document the prevalence of CAC in this race. Secondly, the percentile ranking system used to divide the patients may be more relevant than absolute score ranges that we are accustomed to, as they gauge the individual in relation to his peers and lets him know where he stands.

Some findings need to be further addressed and verified. For example the lack of difference in CAC score between men and women of the same age group, when it is accepted that women generally lag behind men in atherosclerosis development, catching up only after the age of 60 years. The limitations to the methodology were indeed gross. The lack of complete lipid profiles were of particular concern. Because we do not want to be accused of re-inventing the wheel, any practical application of CAC scoring must be additional to current models of cardiovascular risk prediction, of which lipid profile is probably the most important after age and gender.[12] The fact that these patients will not be followed up is clearly a lost opportunity on such a large group of patients to derive prognostic information in the future. Finally the use of a 4-slice MDCT that puts the patient on higher radiation exposure and compels a 30 second breath-hold is a major obstacle. Reconstruction at 1 mm slice thickness for CAC scoring also runs against the norm of 3 mm slice thickness recommended generally.[14]

But where there are gaps and limitations, there are opportunities. And I would urge readers to critically appraise this article and act upon them. We previously published a short article demonstrating that, as a result of CAC scoring and coronary angiography by MDCT, about 30% patients with intermediate cardiovascular risk profile were re-categorized as high risk.[15] More Asian population studies are required. And then perhaps through a united concerted effort that mirrors much of the Caucasian-derived literature that has dominated this editorial and global decision-making, we can address and overcome the shortcomings that ultimately alter the perception on how best to estimate cardiovascular risk in the asymptomatic Asian population. And then finally we know where we stand with CAC scoring by CT.

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Sighting a tiger at Bandhavgarh. *Courtesy:* Dr Lokesh Abrol

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Escalating Coronary Heart Disease and Risk Factors in South Asians

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An epidemic has been defined as the disease that appears as new cases in a given human population during a given period at a rate that substantially exceeds what is expected based on recent experience.[1] Common diseases that occur at a constant but relatively high rate in the population are said to be endemic. Coronary heart disease (CHD) is a new epidemic in South Asia and has very quickly evolved into an endemic and a major health issue.[2]

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In India leading major cause-groups of deaths during 1984 to 1998 have been reported by the Registrar General of India. Trends show that there has been a significant decline of proportionate mortality from infectious diseases from 22% to 16% whereas mortality from cardiovascular diseases increased from 21% to 25% and due to injuries from 8% to 12% ($p < 0.05$).[3] Gajalakshmi *et al*[4] performed verbal autopsy in urban Chennai to determine causes of deaths in 48,357 subjects aged 25-69 years. Vascular diseases were the largest group with 18,680 deaths (38.6%) followed by cancer (8.7%), tuberculosis (5.8%) and respiratory causes (3.5%). Unspecified medical causes accounted for 19,825 (41.0%) deaths. Joshi *et al*[5] reported mortality statistics from Andhra Pradesh Rural Health Initiative. In this study that prospectively evaluated causes of death in a population-cluster of about 150,000 subjects it was reported that there were 1,354 deaths in the first year of follow-up and verbal autopsy revealed that diseases of circulatory system caused 34% of male and 30% of female deaths. These studies show that cardiovascular diseases are major causes of death in Indian urban and rural locations. Though similar data are not available from other regions of South Asia, the situation should not be very different.[6]

Increasing CHD in South Asia

Estimate of the burden of CHD in India and other South Asian countries has been based on indicators from population based cross-sectional surveys.[7] In India multiple epidemiological studies have been performed in urban and rural populations over the past fifty years. The prevalence of CHD in various studies has been reported earlier in this journal.[8,9] Majority of these studies used similar population-based recruitments, methodology and diagnostic criteria (known CHD, Rose-questionnaire angina and/or electrocardiographic (Q-ST-T changes) but the age-groups evaluated were variable and we therefore compared studies that included subjects ≥ 25-30 years to determine secular trends.[10] In subjects ≥ 30 years a high prevalence is consistently observed in studies at urban locations (Chandigarh 6.6%, Rohtak 3.6%, Varanasi 6.5%, Delhi 9.7%, Jaipur 9.2%, Trivandrum 12.6%, Jaipur 9.1%, Chennai 11.0%, and Goa 12.5%) as compared to the rural (Haryana 2.1%, Haryana 2.7%, Punjab 3.1% and Rajasthan 4.3%).[9] There are significantly increasing trends in urban (linear trend, $r^2 = 0.60$) as well as rural ($r^2 = 0.31$) populations. Increasing CHD in India correlates with trends in prevalence of multiple cardiovascular risk factors-smoking, obesity, truncal obesity, hypertension, hypercholesterolemia and diabetes.[10]

Large epidemiological studies in other regions of South Asia are lacking. The Pakistan National Health Survey[11] focused on prevalence of risk factors for communicable and non-communicable diseases and reported a high prevalence of smoking, hypertension and high cholesterol in both men and women. A study on prevalence of CHD using clinical and electrocardiographic criteria similar to those used in Indian studies and reported an alarmingly high prevalence among urban subjects in Karachi.[12] In a cross-sectional study of 320 randomly selected adult subjects aged ≥ 40 years the overall prevalence reported was 26.9% (95% confidence intervals, CI, 23.4-37.5%) with almost equal prevalence in men (23.7%, CI 17.8-30.9%) and women (30.0%, CI 23.4-37.5%). Although the denominators are small, this prevalence is more than any of the studies from India. In the present issue of the journal Zaman *et al* have reported on prevalence of ischemic heart disease in rural Bangladesh.[13] The authors studied 447 adults aged 20 years or older and included subjects with known CHD or those with pathological Q-waves on electrocardiogram. The prevalence was 4.6%

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(CI 1.3-7.9%) in men and 2.7% (CI 0.8-4.6%) in women. Kumar *et al*[14] used criteria similar to those used by Zaman *et al* and reported lower CHD prevalence in rural areas of Punjab. There are no major studies that have evaluated CHD prevalence in other large countries of South Asia such as Nepal, Sri Lanka and Afghanistan. Studies among emigrant South Asians living in Britain[15] have revealed that CHD risk is the highest in Bangladeshi subjects as compared to Pakistanis or Indians but in local epidemiological surveys such differences are not observed. There are multiple limitations of cross-sectional epidemiological studies such as small and variable sample sizes, variable and at-times low response rates, inappropriate diagnostic criteria such as history, non-specific electrocardiographic changes such as abnormal ST-T waves, lack of age-standardization and incomplete reporting of results.[16] To clarify disease-risk factor associations larger prospective epidemiological studies are required in different regions of South Asia.

An important issue highlighted in another article of this journal addresses the issue of CHD among the low socioeconomic status subjects in India. Gupta and Gupta[17] have succinctly summarized currently available information on this topic. Case-control studies in Bangalore,[18] Delhi[19] and the INTERHEART South Asia study[20] have reported that low socioeconomic status defined by low educational status is associated with greater risk of first myocardial infarction. Some epidemiological studies have also reported greater prevalence of cardiovascular risks among the less educated and poor rural[21] and urban[22] subjects. More studies are needed in this direction because India is a poor country and increasing prosperity and adiposity on background of low birth-weight and thrifty phenotype[23] portends a serious cardiovascular disease epidemic.

Increasing Cardiovascular Risk Factors

There have been multiple hypotheses to explain the increase in CHD in the Indian subcontinent. Anecdotal observations and case-control studies in many major hospitals demonstrated that risk factors in cases were not very dissimilar to controls and that there was something unique about atherosclerosis in this group.[6] Evidence from recent case-control studies[18,19,20] and epidemiological studies[10] has demonstrated the importance of traditional risk factors in Indians and South Asians. The case-control INTERHEART study evaluated the importance of multiple risk factors in genesis of first acute myocardial infarction in different regions of the world.[24] In this study 15152 cases of first myocardial infarction were recruited from 52 countries and were compared with risk factor profile in 14820 matched controls. This study identified that nine well known coronary risk factors- abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low fruit and vegetable consumption, low alcohol consumption and lack of physical activity- accounted for more that 90% cases of acute myocardial infarction. An important finding of this study was a younger age of occurrence of acute myocardial infarction in South Asians.[20] The mean age of occurrence of first myocardial infarction among 1732 participants from South Asia was 53.0 ± 11.4 years as against 58.8 ± 12.2 years in other countries. Within South Asia the mean age was the lowest among the Bangladeshi (51.9) as compared to Pakistani (53.3), Indians (53.0), Sri Lankan (57.7) and Nepalese (58.9) subjects. This is in consonance with the risk factor profile studies in emigrees.[15] The risk factors that were found important in the overall INTERHEART cohort were important in the South Asians as well.[20] Some harmful risk factors were more common in South Asians (elevated ApoB/ApoA-1 ratio, diabetes, and lifestyle factors) and all the risk factors occurred at a younger age. Non-smoked tobacco that is peculiar to the Indian subcontinent also emerged as an important risk factor. All these risk factors are dependent on the demographic and societal transitions associated with affluence. These transitions influence physical activity, dietary calorie and fat intake, smoking and tobacco use and lead to generalized and truncal obesity, high blood pressure, diabetes, abnormal lipids, metabolic syndrome and psychosocial stress.[8]

There is epidemiological evidence that many of these risk factors are increasing in India.[10] Jaipur Heart Watch (JHW) studies have systematically evaluated secular trends in risk factors in urban subjects. Comparison of risk factors in population based samples in JHW-1[25] and JHW-2[26] has shown that both in men and women obesity and central obesity increased over a 7-year period associated with increase in prevalence of hypertension, dyslipidemia and diabetes. The third study (JHW-3) was a location based study and reported that obesity was a major determinant of various risk factors.[27] The fourth study in this series is reported in the present issue of the journal.[28] This is a location-specific population based study and reports a high prevalence of multiple cardiovascular risk factors. The important message of this study is disparities in prevalence of risk factors in India, high levels of obesity and truncal obesity in this group, greater prevalence of clinically important cardiovascular risk factors and a strong correlation of obesity (which is a surrogate of reduced physical activity and increased consumption) with these risk factors. Combining the four JHW studies shows that there is a strong association of increasing obesity with increasing hypertension, hypercholesterolemia, diabetes and the metabolic syndrome (Figure). Limitations of these studies include use of different cohorts to evaluate trends, and other issues relevant for cross-sectional studies mentioned above.[16] Evaluation of a single cohort such as the Framingham Study is more accurate for describing secular trends in risk factors although most of the countries use multiple cross sectional studies to determine trends as

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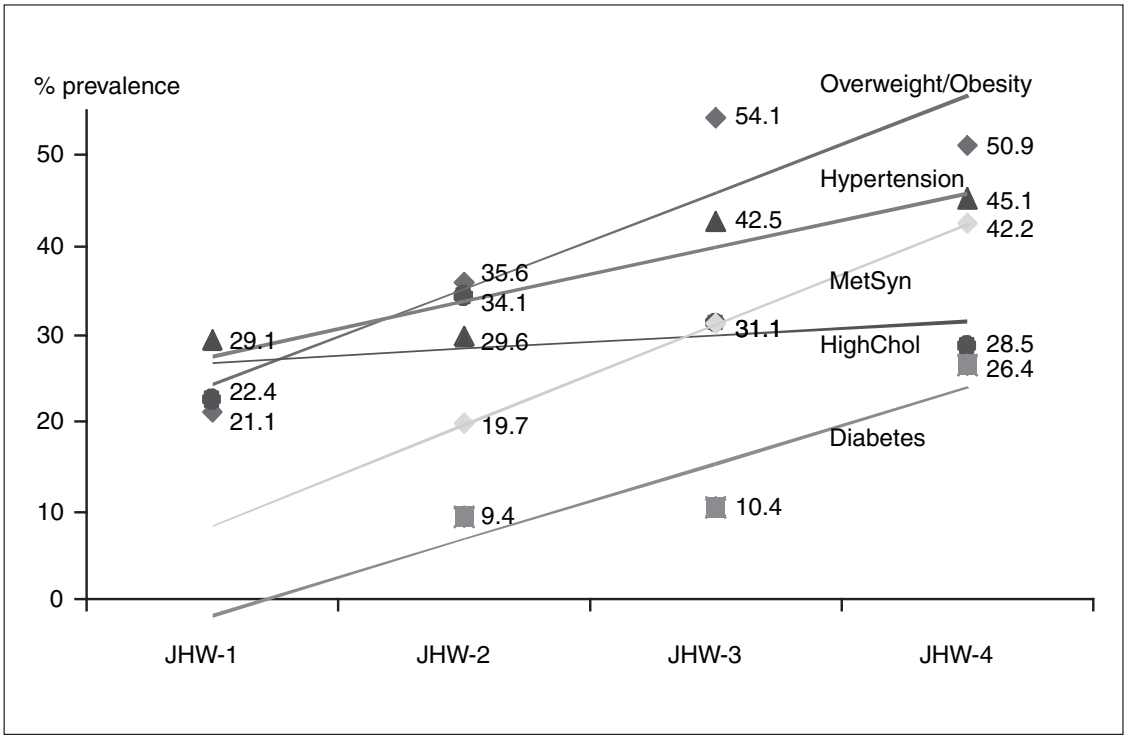

Figure. Correlation of increasing overweight/obesity (body mass index ≥ 25 kg/m^2) with age-adjusted prevalence of multiple risk factors in Jaipur Heart Watch (JHW) studies[25–28] among men 20–59 years. Two-line regression analyses show that there is significant correlation of obesity with hypertension ($r^2 = 0.91$), hypercholesterolemia-total cholesterol ≥ 200 mg/dl ($r^2 = 0.53$), metabolic syndrome ($r^2 = 0.87$), and diabetes ($r^2 = 0.84$).

in the JHW studies.[29] Ongoing prospective studies in India may provide better information on trends in risk factors. In conclusion, these three articles highlight the increasing burden of coronary heart disease and its risk factors in the Indian subcontinent and emphasize the need to contain this epidemic of cardiovascular disease, combat its impact and minimize its toll.

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