Rapid Screening for Subclinical Atherosclerosis by Carotid Ultrasound Examination

The HAPPY (Heart Attack Prevention Program for You) Substudy

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ABSTRACT

Background: Cardiovascular disease (CVD)-related death rates have been escalating in emerging economies such as India. A strategy to initiate prophylactic medical intervention by direct identification of subclinical atherosclerotic burden may be appropriate in rural populations where assessment based on traditional risk factors is not available.

Objectives: This study sought to investigate the feasibility of performing rapid automated carotid ultrasound studies in a rural setting and to measure the prevalence of carotid plaques and age-specific distribution of carotid intima-media thickness (IMT) as an index of subclinical atherosclerosis.

Methods: Screening of the extracranial carotid system with automated B-mode ultrasound was performed along with health questionnaire assessments in 771 asymptomatic volunteers (ages 40 $\pm$ 14 years; 626 men and 145 women) with no known CVD. Measurements of IMT were recorded as the mean of 24 spatial measurements performed over a 1-cm region in the far wall of the common carotid artery at end diastole; the prevalence of the plaque (focal IMT >1.5 mm) was determined.

Results: A total of 69 (8.9%) subjects had atherosclerotic plaques. Of these, 16 (2.1%) exhibited bilateral plaques, 28 (3.6%) left carotid plaque only, and 25 (3.2%) had right carotid plaques. Patients even under 50 years showed a high prevalence of carotid plaques (7%), which increased with age (25% and 35% for 51 to 70 and >70 years, respectively). Only 3 (4.3%) participants with plaques were former smokers. Global mean IMT was 0.55 $\pm$ 0.13 mm and correlated with age for both left and right carotid arteries ($r = 0.61$ and 0.60, $p < 0.001$ for both) in male as well as female subjects ($r = 0.70$ and 0.67, $p < 0.001$ for both), respectively.

Conclusions: Rapid community screening for subclinical atherosclerosis is feasible with automated carotid ultrasound examination and may be beneficial in rural communities of industrializing nations where traditional CVD risk factor data are not yet readily available.

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Cardiovascular disease (CVD) is the most important cause of death and disability worldwide. According to the World Health Organization, 17.5 million people died in 2005 of CVD with the number expected to increase to almost 25 million by 2020. More specifically, there were over 200 million people worldwide with clinically manifest CVD; almost 80% of this global burden emanated from developing countries [1–3]. CVD in India causes 3 million deaths per year, accounting for one-quarter of all mortality and constitutes the most prevalent (>30%) noncommunicable disease. Prevalence rates of CVD in rural populations, although currently somewhat lower than that of urban populations, will continue to rise to 13.5% of the rural population by the seventh decade of age in 2015. The prevalence rates among younger adults, as well as women, are also likely to increase substantially [4]. It is estimated that by 2020, CVD in India will be the most important cause of death and disability. India currently has approximately 41 million people living with diabetes and >118 million people with hypertension. And barring urgent preventive steps, it is expected that the numbers will rise to 70 and 213 million, respectively, by 2020. The myocardial infarction (MI) occur at a much younger age in Indians than in North Americans and Western Europeans [5].

The INTERHEART (Study of Risk Factors for the first myocardial infarction in 52 countries and over 27,000 subjects) identified that 9 coronary risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, low fruit and vegetable intake, lack of modest alcohol consumption, and minimal indulgence in physical exercise) accounted for 90% of the population-attributable risk for acute MI [6]. There is considerable interest in the diagnosis of atherosclerosis when patients are still asymptomatic. Advanced atherosclerosis may exist with minimal or no symptoms, and in more than one-half of the patients, the first clinical manifestation of coronary artery disease may often be catastrophic, including acute MI, unstable angina, or sudden cardiac death [7]. CVD threatens to cripple the younger population in developing countries and retard economic growth. An early detection of atherosclerosis during the subclinical stages of disease might permit the reliable identification of subjects at increased risk of an adverse cardiovascular event, and appropriate therapy (e.g., lipid-lowering) may allow the institution of intervention and may help improve the prognostic outcomes [8]. Grassroot policy measures are available, affordable, accessible, and desirable as methods of intervention [9,10]. The high-level United Nations General Assembly meeting in September 2011 recognized and emphasized development of strategy for promotion of cardiovascular health [11].

In 2001, the National Cholesterol Education Program Adult Treatment Panel III had recommended that the carotid intima-media thickness (IMT) could be used as an adjunct in CVD risk assessment. The finding of atherosclerotic plaque or increased carotid IMT ($\geq$75th percentile for age and sex) could elevate an individual's risk to a higher risk category [12]. It also suggested that appropriately evaluated carotid IMT measurements can better identify persons at higher risk for CVD events than the traditional risk factors can. The definition of atherosclerotic plaque in the context of B-mode ultrasound was subsequently described by the Mannheim Consensus [13].

The present cross-sectional study investigated the burden of subclinical atherosclerosis in a previously unstudied rural northern Indian community that follows a relatively healthy lifestyle including abstinence from smoking and alcohol, exclusively vegetarian diet, indulgence in at least modest physical activity, and meditation. We investigated the feasibility of undertaking a noninvasive determination of carotid plaques and carotid IMT in a large number of subjects in a short time in a rural setting and the age- and sex-related distribution of individuals with subclinical atherosclerosis in extracranial carotid beds. Although historical details were available for all participants and blood pressure was measured in all at the time of carotid examination, biochemical parameters including blood cholesterol and sugar were not available in the camp setting.

METHODS

Study population

This study is a part of a larger initiative, the HAPPY (Heart Attack Prevention Program for You) substudy, which is a multicenter, multinational effort [14] dedicated to mass screening and mass education for the prevention of CVD and promotion of CV health. The HAPPY program in India was started in January 2010 (referred to as TrueHAPPY) in the rural northwestern town of Sirsa, Haryana. In excess of 10 million followers of spiritual leader Saint Gurmeet Ram Rahim Singh Ji Maharaj gather in Sirsa during the third week of January for an annual event [15]. During this spiritual event, a medical camp is conducted at the Shah Satnam Ji Speciality Hospital that allows a unique opportunity for service and research initiatives. This event includes free medical checkups for the followers staffed by physician volunteers. B-mode carotid ultrasound was offered at this gathering over a 4-day period in January 2012 to those participants that provided written consent. The population-based study was approved by the Institutional Review Board of the Shah Satnam Ji Specialty Hospital, Sirsa.

Enrollees were asked to complete a brief questionnaire about their age, sex, family history of CVD, smoking history, and educational level. They were also asked whether they were taking any medications for hypertension or diabetes. Female enrollees were asked if they were pregnant, and those that were, were informed of their ineligibility to participate in the ultrasound examination due to local legal restrictions. Traditional risk-factor assessment was not available for all participants and was the part of the study protocol. The information gathered from the short questionnaire was entered directly to the risk assessment algorithm available on the carotid ultrasound machine (Panasonic CardioHealth Station, Secaucus, NJ, USA).

Automated carotid imaging

A total of 779 asymptomatic participants were scanned over 4 days by fully automated carotid ultrasound technology by previously untrained radiology and cardiology residents who underwent 4-h intense on-the-spot training to learn the imaging technique. Bilateral extracranial carotids were imaged with the subjects lying supine with neck oriented 45° using a custom pillow (provided by the ultrasound manufacturer) in accordance with the clinical protocol recommended within the American Society of Echocardiography Consensus Statement [16]. Presence or absence of plaque in the right carotid was determined by acquiring short-axis (transversal view) B-mode images with a 9-MHz linear transducer. The transducer was manually moved from the base of the neck to the highest segment above the carotid bifurcation that was accessible. The short-axis B-mode images were visually inspected for the presence of any plaques. Plaque was defined as any focal wall thickening greater than 1.5 mm protruding into the lumen of the scanned carotid [13,16]. If a plaque was found, the ultrasound image was marked up with the help of on-board tools. Next, right carotid IMT was measured from a single scan angle, which showed the clearest visualization of IMT and the straightest carotid artery segment. The ultrasound system employed in the current study incorporates a sensor in the transducer that tracks the scanning angle in real time and records the transducer angle position at which the IMT is taken. Although the user is able to make multiple angle measurements at predefined locations (anterior/mid/posterior), to save time, a single-angle measurement at which maximum IMT was obtained was taken. The ultrasound system also tracks the carotid diameter change continuously and determines systole and diastole timing based on vessel lumen diameter changes without requiring an external electrocardiogram. The automated ultrasound system further provides automated measurement of IMT continuously over a 1-cm region of interest (ROI) based on raw radiofrequency data. For IMT measurement, the transducer was moved from the base of the neck toward the bifurcation to align the flow divider with an on-screen vertical marker. This procedure ensures that the ROI is automatically located in the far wall of the common carotid (CCA) approximately 1 cm from the flow divider. Within the 1-cm ROI, the system tracks 24 spatial measurements at 200 frames/s for a total of 4,800 measurements every second. Thus, the reported IMT values from the ultrasound system are an average of 24 spatial measurements over a 1-cm region at end diastole. In a similar manner, the measurements were repeated on the left carotid. In this study, IMT values in the CCA were not classified into percentiles as recommended in the American Society of Echocardiography Consensus Statement [16] because normative reference IMT values are not known to be available for the population studied. Clinical decision-making, therefore, considered only atherosclerotic plaque findings in the carotids.

Inter- and intraobserver variability in interpretation

The feasibility and reproducibility of this automated on-screen carotid ultrasound system (CardioHealth Station) with respect to manual measurement with a conventional system (Acuson Sequoia, Siemens, Malvern, PA, USA) was documented [17] in 50 consecutive patients (age 62 ± 5 years, range 21 to 79 years, 36 men). For each patient, 3 frozen frames of the distal 10 mm of the right and left CCA were acquired on the 2 systems by blinded operators and the average of the mean value of 3 readings of each system was calculated. The correlation coefficient for the interobserver variability was 0.95 and 0.94 for the automated and manual measurements, respectively. The comparative coefficient of variation of the interobserver variability was 8.2% and 8.7% for the automated and manual measurements, respectively. There was no clinically relevant difference between measurements obtained by the 2 systems (intraclass correlation coefficient: 0.98). The acquisition time of the automated system was significantly shorter than that of the conventional system ($p < 0.01$).

RESULTS

A total of 779 subjects participated in the carotid exam evaluation; 8 were excluded from data analysis (1 duplicate, 3 missing left IMT data, 2 subjects below the age of 18 years, 1 image artifact, and 1 IMT measurement not in the far wall of the CCA). Of the 771 subjects (mean age 40 ± 14 years), 626 were men (41 ± 14 years) and 145 women (39 ± 13 years); age distribution by sex is illustrated in Figure 1.

Participants in this study belonged to a community that was primarily involved in active lifestyle practices like tilling fields or performing other labor-intensive work. Based on the responses to the questionnaire, 20 male enrollees identified themselves as former smokers, 22 were on hypertension medication, and 26 were on medication for diabetes. A mere 6 reported family history of CVD. None of the women had ever smoked or reported being on medication for hypertension or diabetes and none reported any family history of CVD.

An analysis of the 771 subjects showed that 69 (8.9%) had atherosclerotic carotid plaques (Fig. 2); the prevalence in the male cohort was higher ($n = 63$, 10%) than in the female cohort ($n = 6$, 4%; $p = 0.02$). Of the 69 subjects found to have plaques, 16 (2.1%) exhibited bilateral plaques (14 men, 2 women), 28 (3.6%) had left carotid plaque, and 25 (3.2%) had right carotid plaques only. Focusing just on the male subjects with atherosclerotic plaques, only 3 (5%) reported

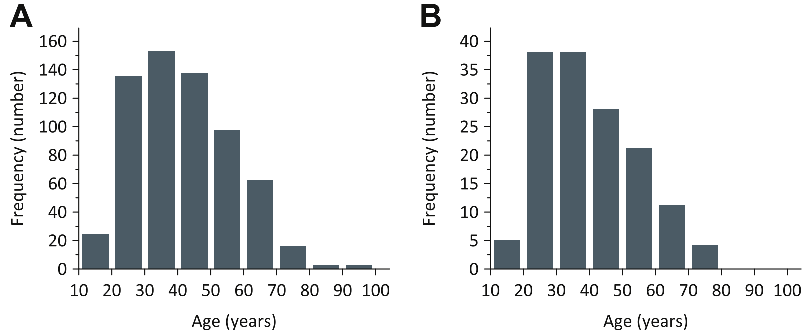

FIGURE 1. Age distribution. Histograms in male (A) and female (B) subjects suggest that the majority of subjects were in the age groups ranging between 18-60 years.

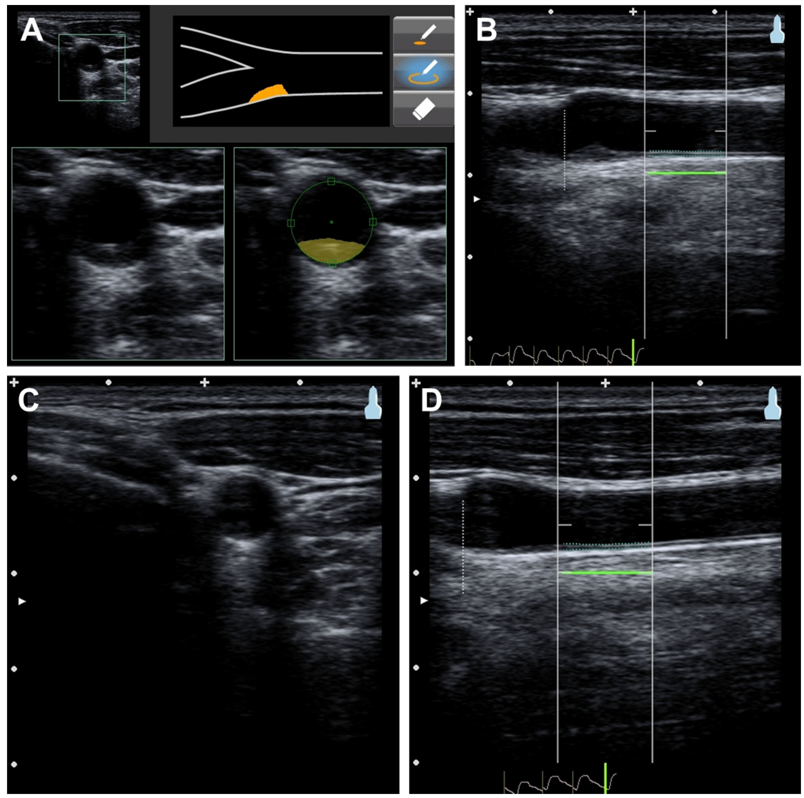

FIGURE 2. Measurements of carotid plaque and intimal-medial thickness (IMT) using B-mode ultrasound imaging. The figure illustrates the assessment of carotid arteries in a 37-year-old male subject. The right carotid of the subject is scanned in the transversal plane (short-axis view) from the base of the common carotid up through the bifurcation. An atherosclerotic plaque was found in the bulb region and this was marked up as illustrated (A). The far-wall IMT of the common carotid approximately 1 cm from the flow divider was then measured and recorded in the longitudinal plane (long-axis view) as illustrated in Figure 4 (B). The exam was repeated on the left carotid, but this time no plaque was identified; the corresponding transversal and longitudinal images, respectively, are illustrated (C, D).

smoking history, 4 (7%) were on medication for hypertension, 4 (7%) were on medication for diabetes, and only 1 (2%) reported a family history of CVD. The prevalence of carotid plaque in subjects even below the age of 50 years was relatively high (7%), and the prevalence increased with age as expected (see Fig. 3).

Global mean IMT for the cohort of 771 male and female subjects was 0.55 ± 0.13 mm. Univariate regression analysis showed good correlation between IMT values and age for both left ($r = 0.61$, $p < 0.001$) and right ($r = 0.60$, $p < 0.001$) carotid arteries in male subjects (see Fig. 4). The corresponding correlation between IMT values and age was relatively better for the female cohort in both the left ($r = 0.70$, $p < 0.001$) and right (0.67, $p < 0.001$) carotid arteries (Fig. 4).

DISCUSSION

The HAPPY ultrasound study

The carotid ultrasound evaluation conducted as a part of the HAPPY study is a large population-based initiative to evaluate the presence and severity of subclinical arterial disease in a rural population of India [14]. The study was undertaken in a population that has never received any preventative health checks or screening; it includes subjects

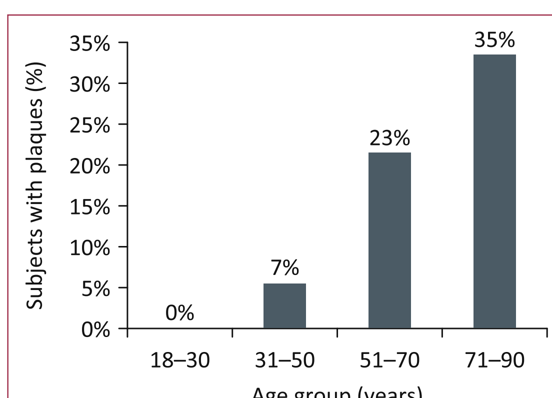

FIGURE 3. Prevalence of carotid plaques by age groups.

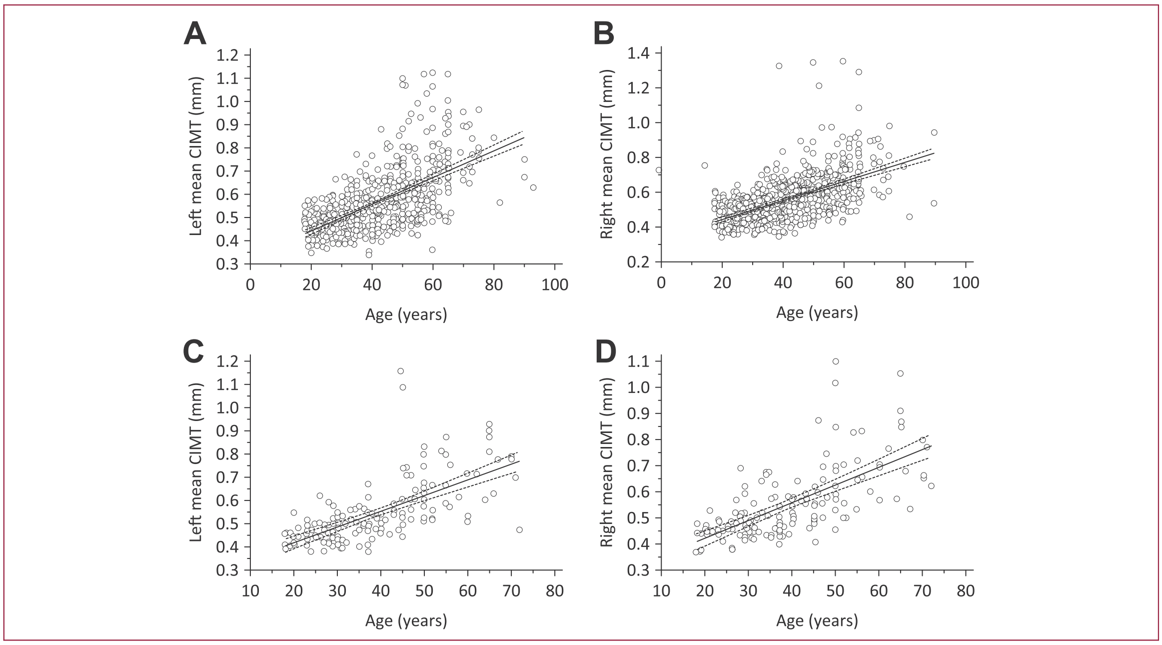

FIGURE 4. Carotid intima-media thickness (IMT) by age. The age-related carotid IMT distributions with linear regression are shown in all men (A, B) and women (C, D).

of all ages and both sexes, and also pre-menopausal women; no formal information was available about traditional CVD risk factors. The study was conducted in a village setting in Sirsa, a north Indian settlement around a spiritual leader Saint Gurmeet Ram Rahim Singh Ji Maharaj. The denizens of the area are permanent dwellers and practice vegetarian diet; no participant currently indulges in cigarette smoking (though some may have been former smokers), and they practice abstinence from alcohol consumption. The participants are a farming community and physically quite active. No reliable data about traditional CVD risk factors are available from this rural cohort. Using an automated ultrasound strategy to screen the carotid arteries to identify atherosclerotic lesions, the prevalence of carotid plaques was found to be 9% in a young cohort with a relatively healthy lifestyle. Even then, the subjects in their 30s, 40s, and 50s revealed a 7% prevalence of carotid vascular disease as represented by the presence of carotid plaques. Furthermore, a progressive increase in the prevalence of disease was noted with each increasing decade. A high prevalence of plaque findings detected at early age groups suggests the compelling value of the novel automated ultrasound screening approach that permits assessments of the entire extent of the carotid arteries from the clavicle up to the carotid bifurcation to the jaw, which may improve the specificity in detecting subclinical atherosclerotic disease.

HAPPY ultrasound study compared with other population studies

It has recently been reported that the carotid plaque burden quantified by ultrasound is better related to coronary artery calcium score than to IMT, ankle-brachial index, and abdominal aorta diameter, and it is expected that the carotid plaque burden will lead to improved prediction of hard events [18]. The systemic nature of atherosclerotic vascular disease is such that various vascular beds simultaneously develop atherosclerotic plaques, including calcium deposits, at different stages of severity [19]. It has been suggested, therefore, that evaluation of greater numbers of vascular beds [20] may allow higher sensitivity for the detection of subclinical disease. It has also been reported that carotid plaque burden may detect early stages of disease even before coronary calcification [18]. This is particularly relevant to the present study because the average age of this cohort was around 40 years when coronary calcium is usually not expected to be as prevalent. Alternative tests such as ankle-brachial index and abdominal aorta diameter represent a much severe disease manifestation at an older age. In a relatively young cohort that includes pre-menopausal women, a coronary calcium score is neither desired nor recommended.

Whereas the volumetric carotid plaque quantification expressed as carotid plaque burden correlated strongly with coronary artery calcium score [18], the CAFÉ-CAVES Study of >10,000 subjects with a 10-year follow-up confirmed that the carotid plaque area was a superior predictor of first acute coronary event than the IMT was [21]. Plaque quantification is an emerging field and will most likely become clinically relevant for monitoring responses to medical intervention [22,23]. However, for making the initial clinical decision about whether to initiate medical intervention or not, the simple binary approach of identifying plaque described in this study may be adequate, especially in a younger population where traditional risk factor assessment may not be available.

The present study did not try to identify the relationship of carotid vascular involvement with the coronary affliction. Nor was the attempt made to readdress the relationship of pre-clinical carotid atherosclerosis and the prevalence of standard biochemical and constitutional risk factors. The present study was designed to evaluate the feasibility of assessment of subclinical atherosclerosis at a mass population level on a time- and cost-effective basis and to identify those subjects that might benefit from prophylactic medical intervention.

Study limitations

A number of study limitations are worth consideration. The study sample consisted primarily of residents of a rural town of Sirsa in northern India who are devout followers of a spiritual leader who actively discourages tobacco product and alcohol usage, and promotes a vegetarian diet, active lifestyles, and meditation. Therefore, the results of this study cannot be generalized to a more diverse Indian population. A comprehensive risk factor assessment was not possible due to the unavailability of serum biomarkers during the fast-paced population-based assessments used for the present medical camp. Similarly, the rapid speed at which ultrasound examination was administered (typical exam time <3 min) by nonexperts (residents, other medical staff trained on the spot) could affect the accuracy of study findings (false positives or negatives). Although IMT data were quantified in the far wall of the common carotid for all the enrollees, it was not possible to derive any clinically actionable information from it because of the lack of known normative tables applicable to this population. Similarly, the prognostic value of atherosclerotic plaques for forecasting future CVD events was not addressed in the present study and would require further systematic investigations.

CONCLUSIONS

Mass screening for subclinical atherosclerosis in remote communities is feasible with fully automated carotid ultrasound imaging. Incidental findings of carotid plaques reported here provide compelling reasons for initiating prophylactic medical intervention. Such a strategy may be beneficial in industrializing nations such as India where assessment based on traditional CVD risk factors may not be widely available or well understood.

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