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Performance of WHO Angina Questionnaire in Measuring Burden of Coronary Heart Disease in Human Isolate Populations

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A B S T R A C T

Isolated human populations represent good candidates for studying genetic and environmental causes of common complex diseases because of their decreased genetic and environmental diversity. The possibility of inexpensive and reliable detection of disease prevalence in such populations is therefore of considerable importance, as comprehensive routine health data and disease registries are rarely available in these populations. In this study, we validated the performance of the WHO Rose Angina Questionnaire (RQ) in measuring the burden of coronary heart disease (CHD) in 9 settlements in these Croatian Adriatic islands. CHD was defined as myocardial infarction (MI) diagnosed by a specialist in the local general hospital, or angina pectoris (AP) by a local general practitioner (GP). The »true« prevalence of CHD in 1,001 adult persons was 10.5%. The results of the RQ screening based on the first 3, 5 and 6 questions were compared with medical record of CHD. Increasing the number of RQ questions from 3 to 6 resulted in decreasing test sensitivity (from 59.0% to 30.5%) and increasing test specificity (from 86.3% to 93.0%) in the prediction of true CHD status. CHD prevalence was overestimated by 76% when subset of the first 3 questions of RQ was used and by 25% when the first 5 questions were used. However, it was underestimated by 10% when the first 6 questions were used. We conclude that RQ is a useful screening method for measuring burden of CHD in isolate human populations, and that the result based on the first 6 questions is a good approximation of the true CHD prevalence in the population, although it should be considered a slight underestimate.

Key words: *humans, isolate populations, burden of disease, prevalence, coronary heart disease, WHO Rose angina questionnaire, screening, validity*

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Introduction

Human isolate populations represent good candidates for studying genetic and environmental causes of common complex diseases, due to decreased genetic and environmental diversity[1,2]. Founder effect, genetic drift and inbreeding are population-genetic phenomena in human isolates that can jointly lead to an increase in the population frequencies of rare genetic variants associated with significantly increased disease risk. Consequently, the prevalence of some complex and monogenic diseases in certain sub-isolates is increased in comparison with the disease prevalence observed in general population[3]. It is therefore important that cheap and reliable methods of estimating disease prevalence in such populations are defined, since comprehensive routine health data and disease registries are rarely available in these populations[2]. Detecting an increased prevalence of some diseases in a specific sub-isolate may also point to the action of a unique environmental or lifestyle risk factor. Rare genetic variants of large effect can have similar effect on increased prevalence, which is desirable characteristic for gene mapping using genetic association studies[4].

Coronary heart disease (CHD) is major cause of death and disability and attracts much attention from biomedical research community[5]. The genetic basis of susceptibility to CHD is subject of much debate and still poorly understood[6]. To begin any population-based investigations of genetic basis of CHD in human isolate populations, a reliable screening method to determine CHD prevalence accurately, rapidly and inexpensively in the field study would be needed. In this paper, we aim to assess the performance of WHO Rose angina questionnaire[7] in estimating burden of CHD in 9 settlements from the Croatian Adriatic islands of Rab, Vis, Mljet and Lastovo. This questionnaire has been used previously to assess burden of CHD in geographic isolates[8–11] and cultural isolates[12,13], but with little reference to its accuracy in predicting the true amount of disease burden in the population.

Materials and Methods

Population sample

The Republic of Croatia has 15 Adriatic Sea islands with populations greater than 1,000 inhabitants[3]. The settlements on the islands are characterized by unique population histories and they have maintained isolation through centuries. The Institute for Anthropological Research in Zagreb, Croatia had investigated demographic history and genetic structure of island populations for last 50 years. Results were reported in over 100 publications in international biomedical journals[14–17]. Recent population genetic investigations of Y-chromosomal and mtDNA polymorphisms have confirmed the conclusions of quantitative anthropological research conducted earlier[18,19]. The potential of this isolate resource for research into disease aetiology was then outlined[3] and confirmed through initial successes in finding genetic basis of previously described monogenic (Mendelian) diseases in these populations[20,21]. Further research was designed to facilitate studying of genetic architecture of common complex diseases of late onset (such as cardiovascular diseases, cancer, diabetes and psychiatric disorders)[22–25].

The sample of the population has been collected through fieldwork during 2002 and 2003. It involved research in 9 settlements from the islands of Lastovo, Vis, Mljet and Rab (Figure 1). They are considered to be geographically the most isolated islands, which facilitated the effects of founder effect and genetic drift on genetic structure of the populations. The

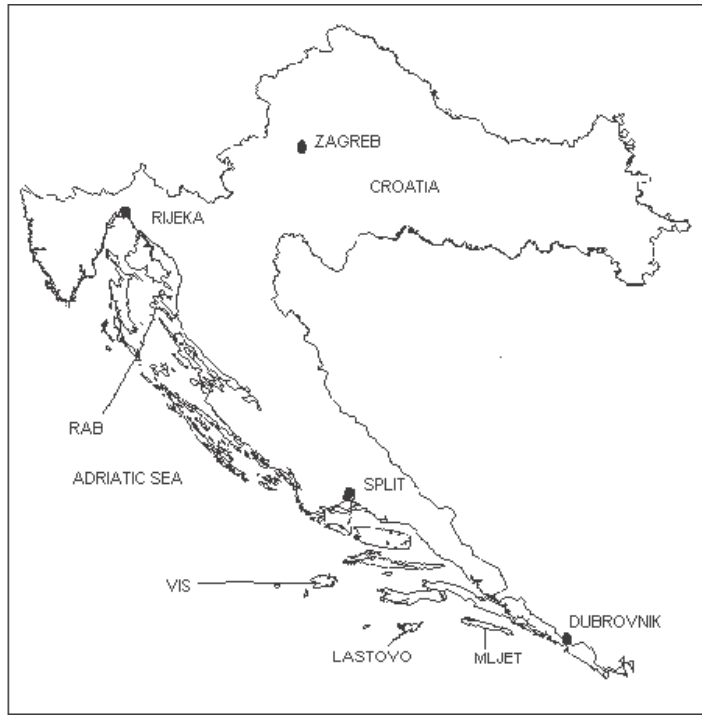

Fig. 1. Geographic location of the investigated islands of Rab, Vis, Lastovo and Mljet.

random sample of 100 adult inhabitants was collected in each of the 9 settlements. Sampling was based on the most complete and accessible population registry in each settlement, which included general practitioner list (Mljet and Lastovo islands), voting lists (Vis island) and household numbers (Rab island). An additional 101 examinees were recruited from immigrants into all 9 settlements, to form a genetically diverse control population. All 1,001 examines were interviewed with WHO Rose angina questionnaire (RQ, see below) by medical doctor, and during interview history of CHD was also obtained from all examines. CHD was defined as myocardial infarction (MI) diagnosed by a specialist in the general hospital, or angina pectoris (AP) by a local general practitioner (GP), as described in an earlier study[25].

Modifications of WHO angina questionnaire to assess CHD burden

We have recently noted[26] that the characteristics of a screening test that make it useful in clinical settings differ from its use in population settings. In clinical settings, it is of primary importance that the screening method show high sensitivity. In measuring disease burden in the population, the key feature of the screening method, such as RQ, is that the number of false positives and false negatives is similar, regardless of test sensitivity and specificity. However, we showed that, over a range of disease prevalences, high specificity of the test is an order of magnitude more important than test sensitivity to correctly assess population prevalence of the disease[26]. As the interplay between screening test sensitivity and specificity

in providing similar number of false positives and false negatives is complex and often counter-intuitive, in this study we aimed to investigate the validity of RQ in prediction of burden of CHD over a range of sensitivity and specificity values.

The values of sensitivity and specificity reported in the literature implied that the use of all 7 RQ questions would result in a considerable underestimate of population prevalence of CHD[26]. Therefore, we validated the performance of RQ in predicting the true CHD burden in the population by using its three modifications: based on the first 3 questions (Q1–3 version), first 5 questions (Q1–5 version) and first 6 questions (Q1–6 version). For details on the questions retained in each modified version, and on how the results of each version were scored, see Table 1. Our expectation was that the modified versions based on fewer questions would be more sensitive and less specific, but that increase in the number of questions will lead to lower sensitivity and greater specificity.

Statistical analysis

We calculated sensitivity (the proportion of those with AP or MI in their medical records correctly identified as positive by questionnaire); specificity (the proportion of those with no diagnosis of AP or MI in their medical records correctly identified as negative by questionnaire); positive predictive value (the proportion of those identified by questionnaire as having CHD who indeed had medical diagnosis of AP or MI), and negative predictive value (the proportion of those identified by questionnaire as not having CHD

TABLE 1
DEFINITION OF THREE MODIFICATIONS OF THE ORIGINAL WHO ROSE ANGINA QUESTIONNAIRE ADJUSTED FOR SIMPLE USE IN VERBAL INTERVIEW TO ASSESS BURDEN OF CORONARY HEART DISEASE IN ISOLATED POPULATIONS. THE INDEPENDENT BACK-TRANSLATION FROM CROATIAN TO ENGLISH IS ALSO PROVIDED

Version	Questions used	Test positive if
Q1–3	Q1: Have you ever had any pain or discomfort in your chest?	Answers as follows: Q1: yes
	Q2: Do you get it when you walk uphill or hurry?	Q2 or Q3: yes
	Q3: Do you get it when you walk at an ordinary pace on the level?	
Q1–5	Version Q1–3 with two added questions:	Answers as follows:
	Q4: What do you do if you get it while you are walking?	As in Q1–3, and: Q4: stop or slow down
	Q5: If you are standing still, what happens to it?	Q5: relieved
Q1–6	Version Q1–5 with one added question:	Answers as follows:
	Q6: How soon?	As in Q1–5, and: Q6: 10 minutes or less
Back-translation from Croatian:	Q1: Do you ever have any pain or discomfort in your chest?	
	Q2: When you walk uphill or hurry, does it produce the pain?	
	Q3: When you walk at an ordinary pace on the level, does it produce the pain?	
	Q4: What do you do if you get it while you are walking?	
	Q5: Do pain or discomfort in your chest go away if you stand still?	
	Q6: How long does it take them to go away?	

TABLE 2
NOTATION AND DEFINITIONS OF TEST SENSITIVITY, SPECIFICITY, POSITIVE PREDICTIVE VALUE, NEGATIVE PREDICTIVE VALUE AND DISEASE PREVALENCE IN THIS STUDY

	CHD present	CHD absent	Total
WHO angina test positive	a	c	a+c
WHO angina test negative	b	d	b+d
Total	a + b	c+d	CHD prevalence: (a+b) / (a+b+c+d)
Test sensitivity: a / (a+b)	Test specificity: d / (c+d)	Positive predictive value: a / (a+c)	Negative predictive value: d / (b+d)

who did not have medical diagnosis of AP or MI) for each RQ modification. Based on those parameters, we computed ratio of test positives to »true« CHD cases in the population under study, which would in ideal case amount to 100%. Information obtained from an interview and medical records could be expressed as a 2×2 table (Table 2) in which »CHD present« and »CHD absent« represent the true state of presence or absence of CHD (based on diagnoses from specialist/general practitioner as described earlier). »CHD test positive« and »CHD test negative« represent the test findings based on the result of each RQ modification, according to the criteria defined in Table 1. Cell »a« represents subjects with CHD (true positives) who test positive, cell »b« subjects with CHD (true positives) who test negative, cell »c« subjects who do not have CHD (true negatives) who test positive, and cell »d« subjects who do not have CHD (true negatives) and test negative. Test sensitivity is given by a/(a+b); specificity by d/(c+d); positive predictive value by a/(a+c); negative predictive value by d/(b+d), and prevalence of CHD by (a+b)/(a+b+c+d) (Table 2). Finally, the ratio of CHD test positives to true CHD cases, which is a direct measure of over/underestimation (in %) of true disease prevalence in the population when each of the RQ modifications is applied, is calculated as sensitivity divided by positive predictive value[26].

Results

The prevalence of CHD in 1,001 studied adult individuals in isolated populations of the islands of Rab, Vis, Lastovo and Mljet, based on medical record from specialists or general practitioners (GP), was 10.5%. Table 3 shows the concordance between definite CHD status and its prediction by the three modified versions of WHO angina questionnaire. The proportion of false negatives increased from 4.3% to 7.3% with adding additional questions to RQ, but the proportion of false positives decreased from 12.3% to 6.3%. Nearly two-thirds of CHD positive cases in population were correctly recognised by modification of RQ based on first 3 questions, but less than a third when 6 questions were used.

Table 4 shows the validity of the three RQ modifications. As predicted, RQ test sensitivity declined from 59.0% to 30.5% with introduction of additional questions, while RQ test specificity increased from 86.3% to 93.0%. Interestingly, positive predictive value of RQ peaked at 37.4% when 5 questions (Q1–5) were used, while negative predictive value was the greatest with 3 questions used (Q1–3). Most

TABLE 3
CONCORDANCE BETWEEN DEFINITE CORONARY HEART DISEASE STATUS AND ITS PREDICTION BY THE THREE MODIFIED VERSIONS OF WHO ANGINA QUESTIONNAIRE, ASSESSED IN 1,001 EXAMINEES FROM 9 ISLAND ISOLATES IN DALMATIA, CROATIA.

	Q1–3	Q1–5	Q1–6
Test positive and have CHD (true positives)	62 / 1001 (6.2%)	49 / 1001 (4.9%)	32 / 1001 (3.2%)
Test negative and have CHD (false negatives)	43 / 1001 (4.3%)	56 / 1001 (5.6%)	73 / 1001 (7.3%)
Test positive and don't have CHD (false positives)	123 / 1001 (12.3%)	82 / 1001 (8.2%)	63 / 1001 (6.3%)
Test negative and don't have CHD (true negatives)	773 / 1001 (77.3%)	814 / 1001 (81.4%)	833 / 1001 (83.3%)

TABLE 4
VALIDITY OF THREE MODIFICATIONS TO THE WHO ANGINA QUESTIONNAIRE ASSESSED IN 1,001 EXAMINEES FROM 9 ISLAND ISOLATES IN DALMATIA, CROATIA

	Q1–3	Q1–5	Q1–6
Sensitivity	59.0%	46.7%	30.5%
Specificity	86.3%	90.8%	93.0%
Positive predictive value	33.5%	37.4%	33.7%
Negative predictive value	94.7%	93.6%	91.9%
Ratio of test to disease positives	1.76	1.25	0.90

importantly, the ratio of RQ test positives to CHD »actual« or »true« positives in the studied population (or TAP ratio – see ref.[26]) was 1.76 when 3 questions were used, 1.25 with 5 questions and 0.90 with 6 questions. This suggests that, due to the highest specificity regardless of the low sensitivity, the RQ version based on 6 questions is best suited to measure the prevalence of CHD in human isolate populations. Caution should be taken as the true population prevalence apparently lies between the estimates based on 5 and 6 questions, so the assessment based on 6 questions should be treated as a slight underestimate.

Discussion

The WHO Rose angina questionnaire (sometimes also referred to as the London School of Hygiene Cardiovascular Questionnaire) is widely used in epidemiological studies as a screening tool and standardised method for assessing CHD burden. It was developed in 1960's for assessment of cardiovascular symptoms in population survey, and since then it has been used in many settings. The validation in former studies generally reported high specificity (80–95%) with variable levels of sensitivity (19–83%)[12,27–29]. Most of the validation studies agree on the usefulness of RQ, but also highlight inaccuracies in cross-cultural assessments, inconsistencies in repeatability, low predictive power of subsequent clinical events, uncertain value of some questions and lack of agreed standard diagnosis which can be used to validate RQ[12,27–32]. The values of sensitivity (30.5%) and specificity (93.0%) obtained with the version ba-

sed on the first six RQ questions in our study, which should be comparable to the reported figures, fall within the expected range.

The estimated prevalence of CHD using the full version of RQ ranged between 2.6% and 23.0% in the studies we reviewed[8–13,27–32], but these estimates related to a variety of different age groups. Studies that report estimates in age groups similar to this study (18 years or older) were rare, as many concentrated on elderly population samples. However, the adjusted comparison shows that the figure of true CHD prevalence of 10.5% in adult population in our study fall within the upper third of the range of previous reported analyses. Our results also imply that the reported results of CHD prevalence measured by full version of the RQ should probably be considered underestimated by 10–20%. This study showed that the value of true population prevalence lies between the results obtained by asking five and 6 questions (of 7) of the RQ. We concluded that using a shortened version of the RQ based on first 6 questions in population studies is adequate to estimate CHD burden in the population not covered by a viable disease registry.

In the future, we aim to apply the modification of RQ validated in this study to determine the age and sex standardised prevalence of CHD in further isolate populations in these Croatian islands. We would then propose to target settlements showing significantly increased prevalence for further study in the expectation that these populations may provide insights into aetiology of this highly complex, multifactorial disease[33,34].

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UČINKOVITOST UPITNIKA SVJETSKE ZDRAVSTVENE ORGANIZACIJE ZA ANGINU PECTORIS U MJERENJU PREVALENCIJE KORONARNE BOLESTI SRCA U IZOLIRANIM LJUDSKIM POPULACIJAMA

S A Ž E T A K

Izolirane ljudske populacije su zahvaljujući smanjenoj genetskoj i okolišnoj raznolikosti prikladne za proučavanje nasljednih i okolišnih komponenti kroničnih nezaraznih bolesti. Zajedničkim djelovanjem populacijsko-genetskih mehanizama poput učinka populacije utemeljitelja, genskog odstupanja i srođivanja genetska raznolikost je smanjena, a učestalosti rijetkih alela s visokim pripisivim rizikom za nastanak bolesti su najčešće povećane. Zbog spomenutih karakteristika i povećane učestalosti nekih bolesti, izolirane populacije su pogodne za mapiranje gena cije mutacije povečavaju rizik od kompleksnih i monogenskih bolesti. Najučestalije bolesti većinom nisu obuhvaćene djelovanjem populacijskih registara, stoga je mogućnost jeftinog i pouzdanog određivanja prevalencije bolesti u takvim populacijama od velikog značaja. U ovom istraživanju, procijenili smo učinkovitost upitnika Svjetska zdravstvene organizacije za anginu pectoris (SZO-AP) u mjerenju prevalencije koronarne bolesti srca (KBS) u 9 naselja na hrvatskim otocima. Definitivna dijagnoza KBS postavljena je dijagnozom infarkta miokarda od strane liječnika specijalista u općoj bolnici i/ili dijagnozom angine pectoris mjesnog liječnika obiteljske medicine. Prevalencija KBS u 1,001 odrasle osobe uključene u istraživanje bila je 10,5%. Rezultati SZO-AP temeljeni na prvih 3, 5 ili 6 pitanja

SZO-AP uspoređeni su s definitivnom dijagnozom KBS. Porast u broju pitanja SZO-AP s 3 na 6 očekivano je rezultirao smanjenjem osjetljivošću screening-testa (s 59.0% na 30.5%) i porastom specifičnosti (s 86.3% na 93.0%). Prevalencija KBS je precijenjena za 76% kada je određivana pomoću prva 3 pitanja iz SZO-AP, a za 25% kada je korišteno prvih 5 pitanja. Kada je korišteno prvih 6 pitanja prevalencija KBS bila je podcijenjena za 10%. Zaključak je da je SZO-AP korisna metoda za procjenu prevalencije KBS u izoliranim populacijama hrvatskih otoka, te da je rezultat testa koji koristi prvih 6 pitanja SZO-AP najbliži točnoj prevalenciji KBS u populaciji.