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Characterising atherothrombosis in Hong Kong: results of the Hong Kong data from a global atherothrombosis epidemiological survey

香港動脈粥樣硬化血栓患者的特徵：全球性流行病學調查結果

Objectives. To describe the characteristics of patients in Hong Kong with or at risk of atherothrombosis, to determine the proportion of symptomatic patients with more than one vascular bed affected, and to assess the relationship between ankle brachial index and disease severity.

Design. Local participation in an international prevalence study.

Setting. Five centres in Hong Kong.

Participants. A total of 210 subjects were recruited (105 women and 105 men). Patients were divided into the symptomatic group (with current or previous atherothrombotic symptoms, n=101) and at-risk group (with no current or previous symptoms, but aged over 55 years with at least two specified risk factors, n=109).

Main outcome measures. Patient characteristics were described, including the number of arterial beds affected, ankle brachial index, presence of risk factors, and medications taken.

Results. Of the symptomatic patients, 30% had more than one arterial bed involved. A total of 55.4% of the symptomatic group and 18.4% of the at-risk group had abnormal ankle brachial index values. Lower ankle brachial indices were associated with a greater number of affected arterial beds. Diabetes mellitus and hypertension were the most prevalent risk factors in the at-risk group. Symptomatic patients were commonly treated with antihypertensive and antiplatelet agents, whereas at-risk patients were mostly treated with antihypertensive and antidiabetic agents. Only 20% of at-risk patients were taking antiplatelet agents.

Conclusions. Ankle brachial index is a useful tool for predicting those at risk of atherothrombosis. This simple measurement can be used as part of the screening process in the general practice. The role of antiplatelet agents in primary prevention of atherothrombotic events in at-risk patients deserves further attention.

目的：描述香港患有或有機會患有動脈粥樣硬化血栓病人的特點、計算多於一處血管床受影響的有徵狀患者的比例，以及評估踝臂指數與病情輕重的關係。

設計：本地患者參與國際患病率研究。

安排：五個醫療中心，香港。

參與者：共210位本地病者成為研究對象，男女各半。病者劃分為兩組，包括患病徵狀組（即目前或曾經出現動脈粥樣硬化血栓徵狀的病人，共101人），以及患病風險組（即從未出現徵狀，55 歲以上且至少受兩種

Key words:
Arteriosclerosis;
Cardiovascular diseases;
Epidemiologic factors;
Hong Kong

關鍵詞：
動脈硬化；
心血管疾病；
流行病學因素；
香港

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致病因素影響的病人，共 109 人）。

主要結果測量：病人的特徵，包括受影響動脈床的數目、踝臂指數、致病因素，以及藥物療法。

結果：患病徵狀組方面，多於一處動脈床受影響的佔 30%。此外，踝臂指數異常的患病徵狀組和患病風險組病人分別佔55.4%和18.4%。踝臂指數愈低，受影響的動脈床數目則愈多。糖尿病和高血壓是患病風險組最普遍的致病因素。患病徵狀組通常服用抗高血壓藥物和抗血小板製劑，患病風險組則大多服用抗高血壓和抗糖尿病藥物，而後者只有 20% 病人服用抗血小板製劑。

結論：踝臂指數能有效推斷病人患有動脈粥樣硬化血栓的可能性，其計算方法簡單，可於普通診症作為其中一項檢查程序。此外，讓患病風險組病人服用抗血小板製劑作為基本的預防措施，也是值得重視的方法。

Introduction

Cardiovascular disease, ischaemic heart disease, and stroke are the leading causes of death worldwide, accounting for 52% of all deaths in 2000.[1] In Hong Kong, heart disease and cerebrovascular disease are the second and third main causes of death, representing 26.8% of all mortalities in the same year.[2] It is now recognised that atherothrombosis is the common factor in all of these conditions. In the past, coronary heart disease, cerebrovascular disease, and peripheral artery disease (PAD) were regarded as discrete localised entities, but they are actually clinical manifestations of the atherothrombosis. Atherothrombosis is an extensive vascular disease affecting the coronary, cerebral, and peripheral arterial beds to varying degrees of severity. The atherothrombotic process is progressive, in which the ruptured or eroded atherosclerotic plaque activates platelets, causing a thrombus formation and resultant vascular injury. Factors in the different arterial beds including blood flow patterns, vessel diameter, and arterial wall structure all affect the precise nature of the atherothrombotic process.[3] The cascade of events leads to various clinical manifestations, such as intermittent claudication, transient ischaemic attacks, stroke, or myocardial infarction (MI).

Individual patients can often have atherothrombosis in more than one arterial bed—in the Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, at least two arterial beds were involved in 26% of patients.[4] Hence, an instance of atherothrombosis would indicate that this pathological process is already manifest in other arterial territories, regardless of whether symptoms are evident or not. Indeed, patients who survive their first atherothrombotic episode have a greatly increased risk of recurrent attacks, whether in the same or separate arterial bed. It has been reported that between 16% and 24% of patients with MI will have a stroke or transient ischaemic attack within 10 years, whereas 25% to 45% of patients who have had a stroke will develop coronary artery disease in the same period.[5] The prevalence of atherothrombosis is increasing worldwide and co-morbidities, such as hypertension, obesity, and diabetes, exacerbate its development resulting in the increased risk of stroke or MI.[6] The well-documented increasing burden of obesity and diabetes worldwide means that effective diagnosis and management of atherothrombosis will become ever more important in future years.

One simple method of predicting atherothrombotic risk is the ankle brachial index (ABI). The ratio of highest ankle pressure divided by the highest brachial systolic pressure is typically between 0.9 and 1.1 in healthy individuals, whereas values below 0.9 indicate atherosclerosis with associated thrombotic risk.[7] Leng et al[8] found that in patients with an ABI of ≤0.9, the relative risk of non-fatal MI, stroke, and cardiovascular death in the 5 years post-baseline was 1.38, 1.98, and 1.85, respectively, compared with subjects whose ABI was above 0.9. This simple, accessible measurement can be useful to warn a patient of the relative risk of atherothrombosis and to indicate the priority for treatment.

A Global ATHerothrombosis Assessment (AGATHA) was an international cross-sectional survey with the objective of better describing the characteristics of patients with or at risk of atherothrombosis.[9] The study described the prevalence with specific risk factors, such as diabetes or hypertension, the number of symptomatic atherothrombotic patients with more than one vascular bed involved, and the relationship of ABI values to disease severity. This paper discusses the results of a subanalysis of the Hong Kong data generated in this study.

Methods

The AGATHA is an international prevalence survey of 8950 patients from 471 sites in 24 countries. Nine countries from Asia participated, which represented

25% of the worldwide recruitment. General practitioners, angiologists, cardiologists, neurologists, diabetologists, internists, and vascular surgeons acted as referral agents. In Hong Kong, 210 patients from five sites were enrolled consecutively from April to October 2002. Patients participated in one study visit, with no subsequent follow-up.

Patient selection criteria

Patients were categorised into one of two groups if they met either of the following criteria:

(1) The symptomatic group, who had previous or current atherothrombotic symptoms, was identified as one of the following: prior ischaemic stroke, transient ischaemic attack, prior MI, history of stable or unstable angina, established PAD, or prior vascular intervention; or

(2) The at-risk group who had no history of a prior event or current symptoms, but was aged 55 years or over with at least two of the following risk factors:

(i) Diabetes mellitus (type 1 or type 2)

(ii) Dyslipidaemia or hyperlipidaemia, defined as recent (≤3 months) with laboratory findings of:
- total cholesterol greater than or equal to 6.21 mmol/L (≥240 mg/dL), or
- low-density lipoprotein cholesterol greater than or equal to 4.14 mmol/L (≥160 mg/dL), or
- high-density lipoprotein cholesterol smaller than or equal to 0.9 mmol/L (≤35 mg/dL), or
- triglycerides greater than or equal to 2.26 mmol/L (≥200 mg/dL), or
- currently using a lipid-lowering agent for dyslipidaemia

(iii) Hypertension, defined as:
- systolic blood pressure ≥140 mm Hg, or
- diastolic blood pressure ≥90 mm Hg, or
- currently on antihypertensive treatment

(iv) Obesity, defined as body mass index (BMI) ≥25 kg/m^2

(v) Current (or former) smoker with consumption of ≥10 pack-years (1 pack-year is equal to smoking 1 pack of 20 cigarettes per day for 1 year, or 2 packs per day for half a year, etc)

Subjects were excluded from the study if they had cerebral disease of non-atherothrombotic origin or neurological signs and symptoms due to non-ischaemic causes (eg neoplasm). Written informed consent was obtained from every participant in accordance with the Good Clinical Practice's requirements.

Data analysis

At each centre, patients were seen by the investigator who recorded their sex, age, race, any history of previous vascular events, any current cardiovascular symptoms, presence of the specified risk factors, and any current medications. Subjects were evaluated by physical examination (weight, height, BMI, heart rate, and blood pressure) and by clinical tests (electrocardiography, ABI measurement, and the optional carotid echo-Doppler, which was performed in only 5.7% of patients in Hong Kong).

Figure legends

Fig 1.

Fig 2.

Ankle brachial index was measured using the ELITE 100R Doppler (Nicolet Vascular, Wisconsin, United States) with one 5-MHz vascular probe—the identical model was used at all AGATHA sites. Training of using this equipment was provided to all participating sites before patient enrolment. The brachial systolic pressure was taken in both arms by use of the Doppler probe in the antecubital fossa. Systolic blood pressure was then recorded at the left and right posterior tibial arteries and dorsalis pedis arteries. The ABI was calculated for each side by taking the highest ankle pressure of each measured side, divided by the absolute highest brachial pressure (from either side). The lower of the two resultant ABI values was used for risk classification. In this study, ABI values ≥0.90 were considered normal, 0.71-0.89 mild obstruction, 0.31-0.70 moderate obstruction, and 0.00-0.30 severe obstruction. A descriptive analysis was performed on patient characteristics and extent of atherothrombosis. Continuous parameters were summarised using mean, median, and 95% confidence interval, whereas categorical parameters were summarised using counts and percentages.

Results

Subject characteristics are shown in Table 1. All participants were Chinese with an equal male to female ratio for the total number of subjects. The median age was 69.6 years, the youngest enrolled patient was aged 36.9 years, and the oldest was aged 91.4 years. The median weight was 59 kg, and the median BMI was 24.5. This index was associated with 'observed risk' for type 2 diabetes and cardiovascular disease in the Asian population.[10] The two groups were very similar in terms of age, weight, height, BMI, heart rate, and blood pressure. Abnormal electrocardiograms were more common in the symptomatic group (60.4% compared with 28.4% in the at-risk group); however, this measurement was not taken in 19% of subjects so that these data were incomplete.

Results from the symptomatic group showed that 29.7% patients had atherothrombosis in two or more

Table 1. Characteristics of Hong Kong patients with atherothrombosis from A Global ATHerothrombosis Assessment survey

Characteristic	At-risk group (n=109)	Symptomatic group (n=101)	Total (n=210)
Sex (male/female) [%]	44.0/56.0	56.4/43.6	50.0/50.0
Age (years)*	68.1 (55.5-87.5)	71.3 (36.9-91.4)	69.6 (36.9-91.4)
Weight (kg)*	59 (37-109)	59 (32-147)	59 (32-147)
Height (cm)*	156 (140-181)	157 (120-179)	157 (120-181)
Body mass index (kg/m^2)*	24.9 (17.4-35.1)	24.2 (14.3-57.6)	24.5 (14.3-57.6)
Heart rate (beats/min)*	70 (47-109)	72 (53-165)	72 (47-165)
Systolic blood pressure (mm Hg)*	160 (105-220)	150 (100-210)	160 (100-220)
Diastolic blood pressure (mm Hg)*	85 (60-110)	80 (50-105)	84 (50-110)
Abnormal electrocardiogram (%)†	28.4	60.4	43.8
Ankle brachial index <0.9 (%)	18.4	55.4	36.2

* Data are expressed as median (95% confidence interval)
† Not performed in 19% of patients

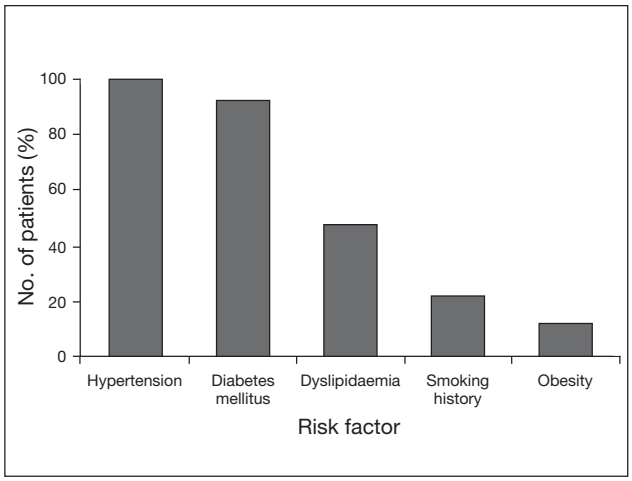

Fig 1. Prevalence of risk factors in the at-risk group
A patient may have two or more risk factors

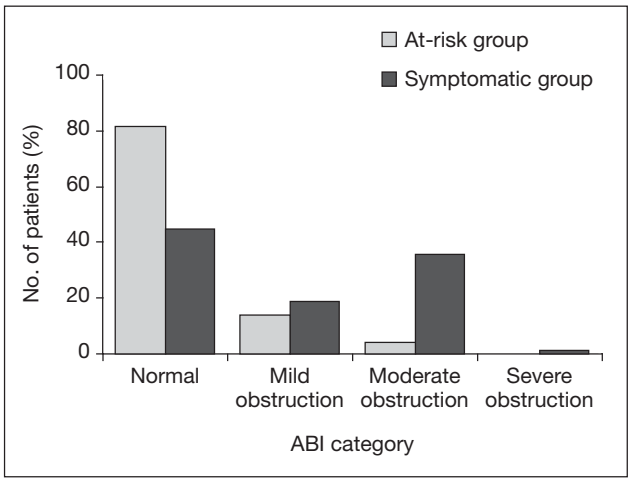

Fig 2. Distribution of ankle brachial index (ABI) in at-risk and symptomatic patients
(i) ABI values: ≥0.90=normal; 0.71-0.89=mild obstruction; 0.31-0.70=moderate obstruction; 0.00-0.30=severe obstruction. (ii) Mild obstruction, moderate obstruction, and severe obstruction come into abnormal ABI category

arterial beds, more than 54% had prior history or current symptoms of coronary artery disease, whereas 43.6% had symptoms of PAD, and 39.6% had a cerebrovascular event. By definition, all the at-risk patients were over 55 years of age and had at least two risk factors; however, the majority of subjects (58.7%) had three or more of the specified risk factors. The overall breakdown of the results was 41.3% with two risk factors, 41.3% with three, 16.5% with four, and 0.9% with five. Of these results, diabetes mellitus and hypertension were the most prevalent risk factors in the at-risk population (Fig 1).

The pattern of ABI results varied between the symptomatic and the at-risk subjects (Fig 2). Among the at-risk patients, 81.6% had normal ABI ratios, and percentage of patients declined steeply when the severity categories increased. In contrast, there was a more even distribution of the symptomatic patients across the abnormal ABI categories compared with the at-risk group (Fig 2). The total percentage of symptomatic patients with an abnormal ABI value was 55.4%, which indicated the further progression of the condition compared with the at-risk group with 18.4% who had abnormal ABI values.

The percentage of symptomatic subjects with abnormal ABI values greatly increased with the number of arterial beds affected (Fig 3). All patients had abnormal ABI values when three arterial beds were affected. Abnormal ABI values were not restricted to patients with peripheral disease; 89% of patients with PAD had an abnormal ABI, whereas 30% of patients without PAD also registered abnormal results. This again indicates that ABI measurement can reflect not only peripheral disease but also systemic atherothrombotic disease.

An analysis of the medications showed that, as expected, the symptomatic group were prescribed more

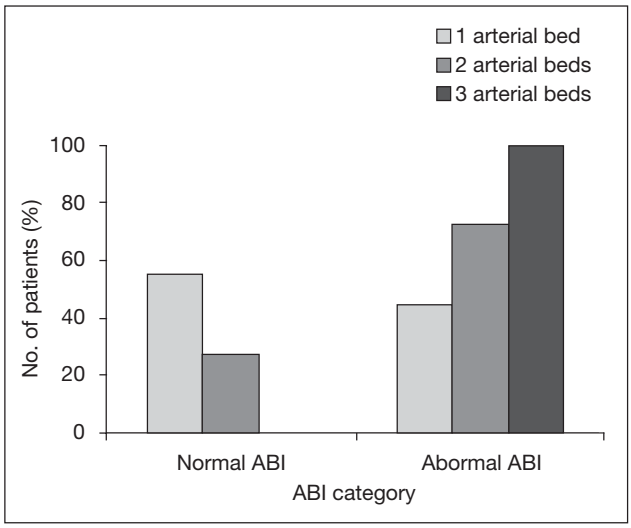

Fig 3. Distribution of ankle brachial index (ABI) in symptomatic patients
The index is inversely associated with the number of arterial beds affected

medications (Table 2) with most taking antihypertensive and antiplatelet agents, whereas half of them were on vasodilators, lipid-lowering or antidiabetic agents. In contrast, the at-risk group were commonly prescribed antihypertensive and antidiabetic agents. Only 20.2% of the at-risk group were on an antiplatelet therapy (acetylsalicylic acid, clopidogrel, ticlopidine or dipyridamole) compared with 85.1% of the symptomatic group.

Discussion

Atherothrombotic disease and its sequelae represent a major health burden worldwide. This burden is predicted to increase globally in the coming decades. The continuing 'westernisation' of diet and lifestyle in Hong Kong and China is leading to increased susceptibility to atherosclerosis.[11] Prevalent risk factors, such as diabetes, smoking, hypertension, and hypercholesterolaemia are commonly found in Hong Kong patients with arterial disease, as demonstrated in this and other studies.[12] Prompt and appropriate management of patients will be increasingly important in limiting the future burden of this disease.

Patients with atherothrombosis often have more than one vascular bed affected. In the current study, 29.7% of Hong Kong patients had atherothrombosis in two or more arterial beds, which was similar to the result of 26% that was reported in the CAPRIE trial.[4] Hence, a diagnosis of PAD should indicate a serious, potentially fatal, and an underlying systemic problem that requires treatment.

Table 2. Percentage of patients taking prescribed medication*

Medication	At-risk group, n=109 (%)	Symptomatic group, n=101 (%)	Total, n=210 (%)
Antihypertensive agents	88.1	86.1	87.1
Vasodilator agents	7.3	51.5	28.6
Antiplatelet agents	20.2	85.1	51.4
Lipid-lowering agents	37.6	51.5	44.3
Antidiabetic agents	89.9	54.5	72.9

* Patients may take more than one medication

Effective treatments for atherothrombosis exist, but there are apparent discrepancies in their application in clinical practice. Patients who have experienced coronary or cerebral events are more likely to receive antiplatelet therapy together with intensive lipid and hypertension treatments compared with those with PAD.[13] Awareness of atherothrombosis associated with systemic disease does not, as yet, appear to have changed treatment patterns—an affected peripheral arterial bed seems to be regarded as a less important indication for treatment than affected cerebral or coronary beds. However, PAD is still a powerful predictor of future MI, stroke, and increased mortality. The 10-year mortality rate of PAD patients with cardiovascular or coronary heart disease is approximately 6 times higher than in healthy controls, and for a subgroup of severely symptomatic PAD patients, the risk is increased to 15-fold.[14]

Screening at-risk patients for atherothrombosis is vital to prevent potentially devastating strokes or heart attacks. The application of ABI measurement as a screening tool has many benefits. Ankle brachial index is an inexpensive, non-invasive, and reliable tool that enables general practitioners to identify patients at risk of atherothrombosis. In this study, 30% of non-PAD patients had an abnormal ABI, and a recent German study of PAD in primary care settings found that approximately every fifth unselected (ie randomly chosen) patient (age-adjusted prevalence, 19.8%) had an ABI of <0.9, indicating generalised atherothrombosis.[15] Compared with angiography, sensitivity and specificity of the ABI is about 90% and 98%, respectively, for a stenosis of 50% or more in leg arteries.[15] Relying on the appearance of symptoms to make the diagnosis, for example, claudication, is not recommended, because classic claudication is found in fewer than 11% of PAD patients.[13] Despite the fact that Doppler ultrasound was used in our study, it is re-assuring to learn from a recent publication by Ostergren et al[16] that ABI obtained by manual palpation of the arterial pulse is clinically valid. Moreover,

a low ABI was a strong predictor of morbidity and mortality in this prospective 4.5-year follow-up study, even if the subjects were asymptomatic.[16]

The cornerstone treatment for patients with atherothrombotic disease (symptomatic or not) should include antiplatelet therapy. Current practice indicates a preference for addressing risk factors including diabetes, hypertension, and elevated cholesterol levels in at-risk patients, whereas relatively few patients receive antiplatelet intervention (only one fifth in the current study). Antiplatelet therapy is a systemic treatment for a systemic disease and shows consistent benefit across all arterial beds in the prevention of secondary atherothrombotic events.[3] However, antiplatelet agents must be used with caution in patients with uncontrolled hypertension or with a history of gastro-intestinal bleeding. The next challenge in the effort to reduce the burden of atherothrombotic events in at-risk patients in our population is to promote the use of primary prevention treatment regimens endorsed by the American Heart Association, the American College of Cardiology, the American Diabetes Association, and the Association of Black Cardiologists.

Conclusion

The results of this survey confirms the assertion that atherothrombosis is a systemic disease, because 30% of symptomatic subjects in Hong Kong had two or more arterial beds affected. Lower ABI values were seen in patients with more extensive atherothrombotic disease; an abnormal ABI was seen in 55.4% of symptomatic group and 18.4% of the asymptomatic at-risk group. An abnormal ABI can be considered a 'red flag' for high atherothrombotic risk, and an appropriate management plan should be formulated to treat such patients—currently, only one fifth of at-risk patients in Hong Kong are treated with antiplatelet agents. Because ABI measurement is quite straightforward, this useful tool can be incorporated into routine screening procedures for patients older than 55 years or otherwise at risk of atherothrombotic events.

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