

健康受測者及冠狀動脈繞道手術 後病人手脈搏波波速的研究

**Hand Pulse Wave Velocity in Healthy Subjects and
Patients After Coronary Artery Bypass Graft Surgery**

研 究 生：徐美政 (Mei-Cheng Hsu)

指導教授：郭正典 (Cheng-Deng Kuo)

施俊哲 (Chun-Che Shih)



國立陽明大學

傳統醫藥學研究所

碩士論文

Master Thesis

Institute of Traditional Medicine

National Yang –Ming University

中華民國九十三年七月

July 2004

健康受測者及冠狀動脈繞道手術後病人手脈搏波波速的研究

摘要

脈診是中醫診斷的重要方法。傳統診脈方法以二十八脈為主要臨床脈象種類，在臨床應用與研究中有很大的侷限性。到現在為止，橈動脈有關脈搏波波速與動脈僵硬度的脈率研究仍很少見。動脈僵硬度的增加是血管病變的病理特徵之一，而且與老化、性別、高血壓和心血管疾病有密切關係。脈搏波波速已被証實是動脈僵硬度的指徵與血管病變的標記之一。因此，本研究的目的是調查手的脈搏波波速(hPWV)如何受年齡、性別與心血管疾病等因子的影響。總計有 146 位健康受測者(72 位男性，74 位女性)及 47 位接受過冠狀動脈繞道手術的冠心病患者(43 位男性，4 位女性)參與本項研究。藉由測量脈搏波傳遞時間和從橈骨莖突到中指指腹中點的距離，並使用下列的公式來計算 hPWV：

$$\text{hPWV (m/s)} = \text{脈搏波橫越的距離 (m)} / \text{傳遞時間 (s)}$$

我們發現年齡是 hPWV 的最顯著的相關因子($p < 0.0001$)。hPWV 隨著年齡的增長而減少，在健康的受測者和 CABG 患者分別是每年減少 0.033 及 0.037 m/s。在多變量線性迴歸分析中，我們發現性別也具有預測 hPWV 的能力($p < 0.001$)，而且男性是一個與 hPWV 增加有相關性並具統計學意義且獨立的預測因子。雖然男性 CABG 患者具有較高的血壓，但與年齡相配的健康男性比較時，兩者的 hPWV 並無明顯的差異。我們的結論是，在健康受測者及已接受冠狀動脈繞道手術之冠狀動脈疾病患者，年齡是預測 hPWV 極顯著的負相關因子，而在健康受測者，性別也是一個與 hPWV 有相關的有意義及獨立的因子；男性 CABG 患者與年齡相配的健康男性，兩者的 hPWV 並無明顯的差異。

關鍵字：脈診；脈搏波波速；動脈功能；老化；性別；冠狀動脈繞道手術。

Hand Pulse Wave Velocity in Healthy Subjects and Patients After Coronary Artery Bypass Graft Surgery

ABSTRACT

Pulse diagnosis is one of the important diagnostic methods in Traditional Chinese Medicine. Till now, there are few studies concerning the relation between pulse wave velocity and arterial stiffness. Increasing arterial stiffness is one of the pathological features of vascular disorders, and is closely associated with ageing, gender, hypertension and cardiovascular disease. Pulse wave velocity is known to be an indicator of arterial stiffness and a marker of vascular disorder. The aim of this study was to examine how was the arterial pulse wave velocity measured at the hand (hPWV) affected by age, gender and cardiovascular disease. A total of 146 healthy subjects (72 men and 74 women) and 47 patients after coronary artery bypass graft surgery (CABG) (43 men and 4 women) participated in this study. The transit time and the distance from the styloid process of the radius to the mid-portion of the 1st phalanx of the 3rd finger were measured, and the hPWV was calculated by using the following formula: $\text{hPWV (m/s)} = \frac{\text{traversed distance (m)}}{\text{transit time (s)}}$. The results revealed that age was the strongest contributor to hPWV ($p < 0.0001$). The decrease in hPWV with age in all healthy subjects and CABG patients was - 0.033 and - 0.037 m/s per year, respectively. Multivariate linear regression analysis showed that male gender also account for the ability to predict hPWV ($p < 0.001$) and is a significant and independent factor associated with increased hPWV. Despite higher blood pressure in male CABG patients, there was no significant difference in hPWV when compared with age-matched healthy men. In conclusion, age is the dominant negative factor contributing to hPWV in healthy subjects and patients after CABG, Gender also is a significant and independent factor associated with increased hPWV in healthy subjects. There is no difference in hPWV between healthy subjects and patients after CABG.

Keywords: pulse diagnosis; pulse wave velocity; arterial stiffness; ageing; gender; coronary artery bypass graft

Contents

中文摘要.....	I
ABSTRACT.....	II
1. INTRODUCTION.....	1
1.1 Pulse diagnosis in traditional Chinese medicine (中醫脈診).....	1
壹 . 傳統中醫脈診及其困境.....	1
貳 . 現代脈診歸類分析研究.....	2
參 . 八維脈法簡介.....	3
一、八維脈象的構成要素.....	3
二、傳統脈法單一脈與複合脈的構成要素分析.....	5
三、八維脈象臨床種類分析.....	5
肆 . 寸口脈八種脈象構成要素的現代科學研究.....	6
伍 . 現代脈象與心血管疾病相關性的研究.....	9
陸 . 近代中醫脈學有關脈搏波傳導速度的動物實驗研究.....	10
柒 . 脈學研究的展望.....	11
1.2 Arterial stiffness.....	12
1.3 Pulse wave velocity (PWV).....	14
1.4 Previous studies and the aim of the study.....	16
2. METHODS	18
2.1 Study subjects.	18
2.2 Study protocol.....	18
2.3 Analysis of hand pulse wave velocity.....	20
2.4 Statistics.....	21
3. RESULTS.....	22
4. DISCUSSION.....	25
5. CONCLUSION.....	32
REFERENCES.....	33

List of tables and figures

Table 1 Clinical and hemodynamic data of male and female healthy controls	47
Table 2 Clinical and hemodynamic data of younger and older male healthy subjects	48
Table 3 Clinical and hemodynamic data of younger and older female healthy subjects	49
Table 4 Clinical and hemodynamic data of male controls and male CABG patients.....	50
Table 5 Clinical and hemodynamic data of female controls and female CABG patients.....	51
Table 6 The change in hPWV with age, SBP, DBP, PP, MAP or body height (univariate linear regression analysis)	52
Figures 1.....	53
Figures 2.....	54
Figures 3.....	55
Figures 4.....	56

1. INTRODUCTION

1.1 Pulse diagnosis in traditional Chinese medicine (中醫脈診)

壹·傳統中醫脈診及其困境

脈診是中醫診斷疾病時特有的診斷方法之一，是中醫臨床上診斷疾病和判斷疾病轉歸、預後的重要依據。脈診充分體現了中醫整體觀念和辨證論治原理，歷來都為臨床醫家所重視，而遺留下豐富的脈學著作。但誠如王叔和於《脈經》之序言中所言：「在心易了，指下難明」¹，傳統診脈方法以二十八脈為主要臨床脈象種類，在實際應用與研究中，都有很大侷限性。中醫臨床脈象千變萬化、十分複雜，二十八脈只是典型的脈象種類，遠遠不能體現中醫臨床脈象的多樣性和複雜性，不利於中醫臨床脈診的學習、應用與研究²。

造成傳統脈診臨床應用侷限性的原因是多方面的。首先是傳統二十八脈本身的侷限性阻礙了臨床脈診的靈活應用及研究。其次是傳統二十八脈的判斷標準缺乏統一性，不同醫師各有習慣，難以對同一病人同一時刻的脈象作出一致的結論³。由於脈診的純粹主觀與經驗性指感，欠缺明確的定量、定性標準，加上脈學古籍中脈象名目與定義繁雜，不只矛盾與衝突所在多見，歷代醫家據以論理診病之學說有許多歧異，對於脈象的分類、描述、分析與理解上亦都屢見差異⁴。

近代以來，中醫脈診學者們已經意識到傳統二十八脈的明顯不足，也曾在

某些綜述性文章中強調脈學理論本身的問題是困境產生的首要原因，必需透過現代科學分類的方法將脈象分類研究的結果加以彙整，重新定義，並規範診脈的標準等，如此將有利於脈象之規範化和客觀化表述²。

貳·現代脈診歸類分析研究

隨著現代科技的進步，如何用現代科學的技術與方法將中醫脈診進行客觀化、科學化及量化的表達，是國內外中醫脈學研究者一直努力的課題。脈象中包含哪些構成要素，或是人的指感是由哪些物理因素共同作用的結果，這是各種不同脈象定義的基礎，也決定脈診科學化研究的內容及方向。近年來，中醫脈學研究者已經認識到脈診科學化必須解決的首要問題是建立一套能明確脈象構成要素的新的辨脈方法，並尋找能夠使脈象構成要素量化的指標³。

為了探索簡明實用、執簡馭繁的診脈方法，有些現代脈學研究者主張用現代脈象分類研究中提出的一些要素或特徵值對脈象進行描述。她們認為提取的脈象要素越完備，對脈象的識別就越精確。目前已知構成脈象的主要因素是脈位、脈寬、脈長、脈率、脈律、脈力、脈流(脈流暢度)、脈體(脈剛柔度)這八個方面，此即北京中醫藥大學王玉來教授所提出的八維脈法³。八維脈法基本已經得到許多脈學研究者的認同³。

參·八維脈法簡介

一、八維脈象的構成要素

北京中醫藥大學王玉來教授提出的八維脈法，他認為若能提綱契領地把握脈象的構成要素，並探索能夠使脈象構成要素量化的指標，將是解決脈診客觀化的關鍵問題。此八種主要的構成要素是：

- (1) 脈位 (A)：代表脈的淺深度。目前通行的診脈方法將脈位分為浮、中、沈三種狀況，但在臨床應用與古人對脈象的描述中，脈位的淺深變化，並不侷限於這三種狀況，因此須將脈位要素再細分為極浮(a1)、浮 (a2)、中 (a0)、沈 (a3)、伏 (a4) 五種不同狀況。
- (2) 脈寬 (B)：代表脈的寬窄度。依照目前通行的診脈方法，將脈寬要素再細分為大 (b1)、中 (b0)、細 (b2) 三種狀況。
- (3) 脈長 (C)：代表脈的長短度。亦按照目前通行的診脈方法，將脈長要素細分為長 (c1)、中 (c0)、短 (c2) 三種狀況。
- (4) 脈率 (D)：代表脈的速度。目前通行的診脈方法，將脈率分為遲、平、數三種狀況，但二十八脈中尚有疾脈，較之數脈，頻率更快。在臨床中亦可見到脈來時快時慢，變化迅速的脈象。因此須將脈率要素更細分為遲 (d1)、平 (d0)、數 (d2)、疾 (d3)、乍急乍緩 (d4) 五種狀況。
- (5) 脈律 (E)：代表脈的節律。按照目前通行的診脈方法，將脈律要素分為無

間歇 (e0)、有規則間歇 (e1)、無規則間歇 (e2) 三種狀況。

(6) 脈力 (F)：代表脈跳的彈力。目前通行的診脈方法將脈力要素分為虛、中、實三種狀況。但在臨床應用與古人對脈象的描述中，脈的彈指力度尚有兩種狀況，如微脈之軟，似有似無，與弱、虛之脈的脈跳無力尚有明顯的區別；再如緊脈之堅硬，彈指有力，與實脈之應指有力亦有明顯的區別。因此須將脈力要素分為極虛 (f1)、虛 (f2)、中 (f0)、實 (f3)、極實 (f4) 五種狀況。

(7) 脈流 (G)：代表脈動的流暢程度。按照目前的通行的診脈方法，將脈流要素細分為滑 (g1)、暢 (g0)、澀 (g2) 三種狀況。

(8) 脈體 (H)：代表脈管張力。也按照目前通行的診脈方法，將脈體要素細分為柔 (h0)、弦 (h1) 兩種狀況。

脈位、脈寬、脈長三者共同反映的是脈的空間性質。脈率與脈律共同反映的是脈的時間性質。脈力、脈流、脈體三者共同反映的是脈的搏動狀態。

其實任何一種臨床脈象都是各類構成要素的綜合表現，即使是平脈也是各類構成要素中正常狀況的綜合。換言之，平脈的脈位是不浮不沉，脈寬是不大不細，脈長是不長不短，脈力是不虛不實，脈率是不快不慢，脈律是均勻規整，脈流是不滑不澀，脈體是柔和不僵。

二、傳統脈法單一脈與複合脈的構成要素分析

按照傳統脈法分析二十八種脈象，將浮、沈、伏、遲、數、疾、虛、實、弦、滑、澀、大、細、長、短、代等十六種稱作“單一脈”，其餘洪、緊、革、牢、散、芤、弱、微、濡、動、促、結等十二種脈稱作“複合脈”。而二十八脈互相組合，更屬複合脈範疇，如浮數、沈弦滑數等脈。

傳統所稱的單一脈是一類構成要素的異常狀況與七類構成要素的正常狀況的綜合表現。傳統的複合脈是多種構成要素異常狀況的綜合表現。如沈弦數脈即是脈位沈、脈寬不大不細、脈長適中、脈力適中、脈率數，脈律齊，脈流是不滑不澀，脈體弦的表現。

三、八維脈象臨床種類分析

八維脈象最大的優點是能夠極為方便地表述數以百計，乃至成千上萬的臨床脈象種類，並可囊括傳統的二十八脈。由於八維脈象的因子有二十九個之多，每類脈象構成要素的因子不能互相組合（如浮與沈、遲與數，不能同時出現），這是各類要素的臨床表現的唯一性。同時，每類要素不能出現某個要素的空缺，這是各類要素的臨床表現的必然性。而每類要素當中的任何一種狀況都可以與其他要素當中的任何一種狀況同時出現，這是各類要素之間的組合性。因此，根據機率論的計數基本原理即乘法原理，八維脈象臨床種類的理論估計值（MS）共有 20250 種，可用如下方法計算：

$$MS = A \times B \times C \times D \times E \times F \times G \times H$$

$$= 5 \times 3 \times 3 \times 5 \times 3 \times 5 \times 3 \times 2$$

$$= 20250$$

可見八維脈象是千變萬化的，能充分體現了中醫臨床脈象的多樣性和複雜性，克服了二十八脈的局限性。八維脈法是一種執簡馭繁的辨脈方法，它從脈象的構成要素入手，採取統一的標準收集脈象資訊，綜合歸納，得出脈診的最終結論。另外，八維脈法以學習與操作的單純性和簡易性來表達臨床脈象的多樣性和複雜性，對中醫脈診的臨床應用、規範化及科學研究，都可產生正面的作用。



肆、寸口脈八種脈象構成要素的現代科學研究

近年來，中醫脈診學者對寸口脈脈象八種構成要素的脈學研究已有一些成果，分述如下：³

1. 在脈位的研究方面，有學者以健康青年為對象，用冷熱刺激的方法建立了脈浮變和脈沈變的脈診模型，結果表明脈浮變時寸口橈動脈的徑向擴張和軸心位移均增大，但以徑向擴張為主。直徑和面積明顯增大，橈動脈血管上層組織的厚度稍減或不變，寸口處的最大血流速度、平均血流速度和加速度有所減小，脈波傳播速度減慢說明與血管有關的

組織彈性模量下降，組織順應性增大。脈沈變時橈動脈徑向擴張減小，血管口徑和面積減小，軸心位移度減弱，橈動脈血管周圍組織張力增大，橈動脈血管上層組織厚度增加。脈波傳播速度加快，血流速度與加速度及加速時間明顯減慢，阻力指數增大。

2. 有關脈寬的研究方面，脈形的大小與脈管的直徑以及脈管的三維運動有關，脈形大者脈管的徑向擴張較大，軸心位移程度高；脈形小者徑向擴張相對小，但軸心位移可以小或者不小。還有研究表明：細脈與非細脈比，寸口橈動脈收縮期及舒張期內徑明顯減小，平均血流速度及血流量均明顯小於非細脈組。
3. 對脈長的研究，研究結果認為脈體的長短首先取決於先天稟賦。脈體長者，橈動脈在寸、關、尺三部的搏動範圍較大，軸向伸長量也大；相反，脈體短者所測的搏動範圍和軸向伸長量均較小，脈體的長短與橈動脈中的血流速度有關，脈長者多卜勒血流各值均較大，脈短者都卜勒血流各值均較小。
4. 有關脈率的研究，有學者採用生理學常用的激發試驗造成脈數變和遲變的模型，結果脈數變組阻力指數 RI 增大，最大血流速度、平均血流速度以及血流加速度與自身對照相比均有增大；脈遲變時最大血流速度，平均血流速度以及血流加速度與自身對照相比均有減小，RI 減小。
5. 對脈律的研究，認為橈動脈局部和全身的血流動力學各參量，在脈律

不齊時並無特定的必然規律，全身或局部的生理或病理變化是通過與脈的至數、節律配合的位、形、勢等具體屬性表現出來的。但提出脈律不齊發生後寸口局部的血管運動情況，血流動力學改變是否仍有規律可尋，須從大量臨床資料的測量分析中找答案。

6. 在脈力的研究方面，通過對脈診人體模型和臨床典型病脈的研究，發現脈實變時橈動脈徑向擴張率、軸向伸長、管壁的搏動範圍以及軸心位移程度均較大，與實變時血流速度快，特別是加速度的增大有關。脈虛變時徑向擴張小，管徑的橢圓程度較大，軸心位移可以減小或增大，與血流速度和加速度減小有關。
7. 對脈流（脈流利度）的研究方面，有研究表明澀脈患者及滑脈孕婦寸口脈的血流量、血流速度、及管腔內徑，經與健康對照組比，澀脈患者的血流量、血流速度、及管腔內徑均明顯減小，滑脈者血流速度、管腔內徑明顯增大。還有結果表明滑脈的血流速度及加速度均較平脈為高，阻抗指數接近正常。對滑變模型及病理滑脈的研究表明，脈滑變時脈管的徑向擴張率大，其血液動力學改變以阻力的下降為主要特徵，並檢測到脈滑變時脈位常偏浮，脈率常偏效，脈勢常偏盛。
8. 有關脈體（脈緊張度）的研究較多，但結論並不一致。目前結果較一致的是認為弦脈組的血流收縮期最大峰值流速、平均流速、血流加速度較非弦脈組高，橈動脈內徑增大，血流量也增加，有關阻力指數，

有研究認為高血壓病弦脈組較高血壓病非弦脈組減小。還有研究認為弦脈組的阻力指數 RI 高於非弦脈組，且舒張期峰值流速低於非弦脈組。這些研究結果的差別可能與樣本來源有關。

伍、現代脈象與心血管疾病相關性的研究

現代醫學範疇之心血管疾病與脈象之關係至為密切。心血管功能狀態的變化可以產生不同的脈象資訊，形成各種脈象。因此，瞭解現代脈診之最新研究成果將有助於提高中醫臨床上心血管疾病診斷的準確性。現將目前脈象與心血管疾病的相關性研究分述如下：

現代醫學對高血壓病不同辨證分型的壓力脈圖分析較多，結果表明大部分高血壓病人的脈搏波形與弦脈的圖形一致，脈圖參數的改變隨高血壓分期的不同而不同。還有研究結果認為高血壓辨證分型的各組脈圖參數也有所不同，因此認為測定脈象圖不僅可以作為高血壓病分期的輔助診斷方法，也為同病異證、異脈提供了依據³。

對冠狀動脈心臟病及心肌梗塞的脈象研究顯示急性心肌梗塞時弦脈比例少於冠心病，而滑脈、弦滑脈比例較大。病態性竇房結綜合徵患者以遲脈、虛脈、細脈為多³。另外，有學者分析 135 例冠心病的中醫證型及脈象，他們指出冠心病可出現滑、弦、細、緩、結、沈、遲、促、澀、浮、數等十一種脈像，其中以滑、弦、細、緩為多，並指出其中原因在於冠心病存在著不同程度的心

功能受損，在不同的疾病中，將產生不同的脈象⁵。

對風溼性心臟病患者的脈象研究發現單純性二尖瓣狹窄的患者脈象主要表現為弦脈，二尖瓣狹窄合併二尖瓣反流或反流的患者，脈象主要表現為滑脈或弦滑脈，中度以上的二尖瓣狹窄合併中度以上的主動脈瓣狹窄的患者表現為澀脈³。

對細脈者的左心室舒縮功能進行的觀察顯示以滑脈和平脈為對照組進行對比研究，結果發現細脈者存在著明顯的左心室舒縮功能的減退，與滑脈和平脈組比較，八項左心室舒縮功能的指標都有高度顯著性差別，說明左心室舒縮功能的減退是細脈產生的重要原因³。

對遲脈與數脈患者的心功能檢測發現，兩組患者均有左心功能損傷，遲脈組心收縮力指數和心指數明顯降低，左心室射血時間延長，總外周阻力增高，血流緩慢。數脈組左心室射血時間縮短，動脈順應性降低，總外周阻力降低，血流加速³。

陸、近代中醫脈學有關脈搏波傳導速度的動物實驗研究

脈搏波傳導速度是反映血流動力學狀態的一項相關指標，主要與血管壁的彈性模量、血管充盈度、管壁的舒縮狀態等因素有關。在脈圖上主要反映重搏前波出現的時間，因此與主波後沿的形態密切相關⁶。

有學者⁷觀察了狗的實驗性弦脈組及滑脈組的脈波傳導速度，測量各組狗的頸

總動脈、股動脈、肘動脈脈搏的Q0時間和主動脈瓣(體表投影點)至各檢測點距離(校正值)，計算和比較各組脈波平均傳導速度。結果實驗性弦脈組、滑脈組兩組脈波傳導速度均高於正常對照組($P < 0.001$)，與動脈收縮壓、舒張壓以及平均壓均有非常顯著的關係($P < 0.01$)。滑脈組的脈波傳導速度還與心率、心輸出量關係非常密切($P < 0.01$)，除肘動脈弦脈組脈波外，其餘各組脈波傳導速度主要與全血容量、血管緊張度等因素有關。

柒、脈學研究的展望

雖然脈象研究近年來發展快速，但是由於中醫脈象研究涉及的範圍極廣，不僅與中醫傳統理論、臨床醫學、生理學等相關，而且與現代數學、流體力學、生物物理學及電機工程等也有相當密切的關係。因此，若能結合現代科技發展，總結前人的脈學研究經驗，並用現代脈象分類研究中提出的一些要素或特徵值對脈象進行描述，則中醫脈診的神秘面紗終將被揭起。

1.2 Arterial stiffness

There is a growing awareness that abnormal artery function plays an important role in the pathogenesis of cardiovascular disease. It is known that arterial stiffness increases with age, and is enhanced in subjects with hypertension, diabetes mellitus, atherosclerosis, and end-stage renal disease. The most obvious consequences of arterial stiffening are increased pulse pressure caused by high systolic blood pressure (SBP) and low diastolic blood pressure (DBP), thereby causing increased left ventricular afterload and altering coronary perfusion. High SBP and pulse pressure, low DBP, and left ventricular hypertrophy have been identified as independent factors of cardiovascular morbidity and mortality in the general population.^{8;9}

Arterial stiffness can be affected by both structural and functional changes in the artery.¹⁰ Structural changes consist of the changes in the composition of the arterial wall; they correspond to vessel damages or adaptations and are important predictors of mortality.¹⁰ They probably represent the major goals for therapeutic intervention. Functional changes in the artery also affect pulse wave velocity (PWV). For instances, the arterial stiffness of a given artery varies as a function of its internal pressure.¹¹ This effect is important because it accounts, at least partly, for the apparent beneficial effect of blood pressure lowering on PWV.

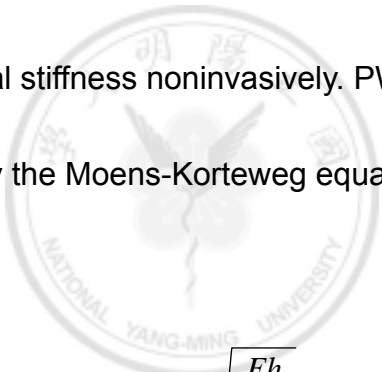
Windkessel theory treats the circulation as a central elastic reservoir (the large arteries), into which the heart pumps, and from which the blood travels to the tissues through relatively nonelastic conduits (peripheral arteries).⁹ The proximal large arteries, such as the aorta and its major branches, can be differentiated from the more muscular conduit arteries, such as the radial and brachial, and the smaller predominantly muscular peripheral arteries. The elasticity of the proximal large arteries is the result of the high elastin to collagen ratio in their walls, which progressively declines toward the periphery.⁹ The increase in arterial stiffness that occurs with age is largely the result of progressive elastic fiber degeneration.¹²

The elasticity of a given arterial segment is not constant but instead depends on its distending pressure.⁹ As distending pressure increases, there is greater recruitment of relatively inelastic collagen fibers and, consequently, a reduction in elasticity. The background level of distending pressure in the circulation is determined by the mean arterial pressure (MAP). This is important because MAP must be taken into account whenever measurements of arterial stiffness are made so that anticipated effects of distending pressure can be differentiated from real differences in the elasticity of the arterial wall. In addition to collagen and elastin, the endothelium^{13;14} and arterial wall smooth muscle bulk and tone^{15;16} also influence elasticity. A number of genetic influences on arterial

stiffness have also been identified. Thus, polymorphic variation in the fibrillin-1,¹⁷ angiotensin II type-1 receptor,¹⁸ and endothelin receptor¹⁹ genes are related to stiffness. The angiotensin-converting enzyme (ACE) I/D polymorphism has been associated with stiffness,²⁰ but not consistently.¹⁸

1.3 Pulse wave velocity (PWV)

PWV, the velocity of the pulse wave to traverse a given distance between 2 sites in the artery, is one of the classical indices of arterial stiffness, and can be used to assess the arterial stiffness noninvasively. PWV increases with arterial stiffness and is defined by the Moens-Korteweg equation


$$PWV = \sqrt{\frac{Eh}{2\rho R}} ,$$

where E is Young's modulus of the arterial wall, h is wall thickness, R is arterial radius at the end of diastole, and ρ is blood density.⁹ Arterial pulse waves can be detected by using pressure-sensitive transducers,²¹ Doppler ultrasound,²² applanation tonometry,²³ or MRI.²⁴

Increases in distending pressure increase PWV.⁹ Therefore, account should be taken of the level of blood pressure in studies that use PWV as a

marker of cardiovascular risk or as a measure of the effects on arterial stiffness of interventions that reduce BP. Heart rate has also been reported to influence PWV. In one study an increase in heart rate of 40 beats per minute increased PWV by >1 m/s,²⁵ a difference that may be relevant to the assessment of cardiovascular risk. Elevated PWV occurs with a range of established cardiovascular risk factors,²⁶ including age,²⁷ hypercholesterolemia,²⁸ type II diabetes,²⁹ and sedentary lifestyle.²⁷ In hypertension, carotid-femoral PWV is an independent predictor of both cardiovascular and all-cause mortality.³⁰ In contrast, pulse pressure (PP) was independently related to all-cause mortality but only marginally related to cardiovascular mortality, indicating that specific assessment of arterial stiffness, with PWV, may be of greater value in the evaluation of risk.

In hypertensives without a history of overt cardiovascular disease PWV also predicts the occurrence of cardiovascular events independently of classic risk factors.³¹ Once again, PP was of predictive value in univariate but not multivariate analysis. Aortic PWV >13 m/s is a particularly strong predictor of cardiovascular mortality in hypertension.⁸ Recently published data show that carotid-femoral PWV increases at a faster rate in treated hypertensives than in normotensive controls, although where BP was well controlled PWV progression was attenuated.³² Aortic PWV, assessed by using Doppler flow recordings, also

independently predicts mortality in patients with end-stage renal failure (ESRF), a population with a particularly high rate of cardiovascular disease.^{33;34} The benefit associated with BP control in ESRF, either by adjustment of dry weight or the use of antihypertensives, was independently related to change in aortic PWV, such that a reduction in PWV of 1 m/s was associated with a relative risk of 0.71 for all-cause mortality.¹⁰

1.4 Previous studies and the aim of the study

Arterial stiffness has gained greater interest because of recent important observations that it is an independent predictor of cardiovascular mortality.^{33;35;36} The study of Taniwaki et al.³⁷ has shown that stiffness index β of femoral artery was closely associated with symptoms of lower limb peripheral artery disease independent of femoral artery intima-media thickness in those with type 2 diabetes. A recent study by Suzuki et al.³⁸ demonstrated that brachial-ankle PWV correlated inversely with blood flow at the popliteal artery in patients with type 2 diabetes. Thus, PWV at different regions may have different clinical significance in cardiovascular diseases.

Although many studies describe that age and type 2 diabetes are significant factors that affect stiffness of aorta,^{29;39} carotid,⁴⁰ brachial,⁴¹ femoral,⁴⁰

and the lower-limb⁴² arteries, only a few studies examined the relative impact of age⁴³ on arterial stiffness in the peripheral arteries. Also, little is known about sex-related difference in regional PWV or stiffness of peripheral arteries.⁴⁴

Because the objective index of pulse velocity in the Eight Aspects of Pulse can be expressed by the pulse wave velocity, and because so far the information is limited regarding the relation between pulse velocity and arterial stiffness, the purpose of the present study was to examine whether pulse wave velocity in the arteries at the hands is affected by age, gender and cardiovascular disease.



2. METHODS

2.1 Study subjects

Both healthy subjects and patients after coronary artery bypass graft (CABG) for more than one year were included in this study. The healthy subjects were recruited from the staff in Taipei Veterans General Hospital and nearby community. The following subjects were excluded from the study: using medication for cardiovascular disease, hypertension (defined as SBP > 140 mmHg, DBP > 90 mmHg), or obesity (defined as a body mass index (BMI) > 30 kg/m²). CABG patients were recruited from the outpatient service of the Division of Cardiovascular Surgery, Department of Surgery in Taipei Veterans General Hospital. The following patients were not included in the study: more than mild valvular heart disease, atrial fibrillation, significant limb tremor, deformation of limbs or digits and history of mild CVA. This study has been approved by the Institute Review Board of the Hospital, and informed consent was obtained from every subject participating in this study.

2.2 Study protocol

All measurements were performed at about the same time of the day

(14:00 to 17:30) to avoid the effects of circadian rhythm on pulse wave velocity.

All subjects were requested not to drink caffeinated beverages for at least 24 h before pulse wave recording. Body height and weight were first recorded, then the blood pressures were measured by using a validated, automated wrist blood pressure monitor (Omron R3, Omron Healthcare Co., Tokyo, Japan), with the cuff kept at the level of the heart during blood pressure measurement. PP and MAP were determined mathematically by using standard formulae. A 10 minutes' rest was routinely requested before this study. The subject was requested to relax and breathe normally in sitting position. If there was any sign or symptom of intolerance to the sitting position such as restlessness, dizziness or pallor, the recording was discontinued. A data acquisition system with sixteen channels (ML795 PowerLab/16sp, ADInstruments, Sydney, Australia) was employed to record the pulse wave signals from both hands simultaneously. The distance from the styloid process of the radius to the mid-portion of the 1st phalanx of the 3rd finger at both hands was measured. Bilateral pulse wave were recorded at a sampling frequency of 4000 Hz for 1 min, and the recorded data were transmitted to the computer for recording and subsequent analysis of pulse wave velocity at the hands (hPWV). The recorded data were processed off-line.

2.3 Analysis of hand pulse wave velocity

The recorded data were processed off-line using purpose-built algorithms developed in Matlab 6.1 (The MathWorks Inc., Natick, Massachusetts, USA). In the initial pre-processing stage, the signals were smoothed and excessive low-frequency baseline variations were removed. These filters did not introduce phase delays or distortion to the waveforms and allowed reliable recognition of the signal peaks. The distance Δx from the styloid process of the radius to the mid-portion of the 1st phalanx of the 3rd finger were measured and the transit time was assessed as the time interval Δt between the peak of the pulse wave detected at the styloid process of the radius and the peak of the pulse wave detected at the mid-portion of the 1st phalanx of the 3rd finger (An example of the transit time timing measure is shown in Figure 1), then the hPWV was calculated by using the following formula:

$$\text{hPWV} = \Delta x / \Delta t$$

The average of both right and left hPWV was calculated from 20 consecutive good quality pulses at each site.

2.4 Statistics

Values are expressed as mean \pm standard deviation (SD). Statistical analysis was performed using SigmaStat (SPSS Inc., Chicago, IL, USA) software packages. The differences in the mean values within group were compared by using Wilcoxon signed rank test or paired t test if appropriate. The differences in the mean values between the two groups were compared by using Mann-Whitney rank sum test or unpaired t test if appropriate. Numerical correlations were analyzed by Spearman rank order correlation coefficient. If statistically significant, the univariate effect of each was also calculated. The effects of age, gender, heart rate (HR), body height, body weight, BMI, SBP, DBP and MAP were assessed by multivariate linear regression analysis. Correlation analysis was used to determine if these effects were independent or not. A P value < 0.05 was considered statistically significant.

3. RESULTS

A total of 146 healthy (72 men and 74 women) and 47 CABG patients (43 men and 4 women)(after CABG for 3.9 ± 2.1 years) were included in this study. Figure 2 shows the hPWV in 146 healthy and 47 CABG subjects. There were no statistical difference in hPWV between right and left hands in either controls or CABG patients. Therefore, the average value of the hPWV of both right and left hands was used in subsequent analyses.

Table 1 compares the hPWV and hemodynamic data in age-matched male and female controls. The body height, body weight, BMI, SBP, PP and hPWV were significantly lower in female controls. The effects of age, gender, HR, SBP and DBP on hPWV were further assessed by using multivariate linear regression analysis, and the result is

$$\text{hPWV} = 5.529 - (0.0316 * \text{Age}) + (0.746 * \text{Gender}) - (0.00767 * \text{SBP}) + (0.0107 * \text{DBP}) + (0.00292 * \text{HR}),$$

with $r=0.544$ and $p<0.001$ (gender: male for 1, female for 0). This equation of multivariate linear regression showed that age and gender could account for the

ability to predict hPWV, and were thus two major determinants of hPWV.

To see the effect of age on hPWV, we divided the male controls into a younger (< 60 years of age, n=49) and an older (\geq 60 years of age, n=23) groups, and the clinical and hemodynamic data of these two groups of subjects were showed in Table 2. It can be seen that the SBP, PP, MAP, and hPWV were significantly increased while the hPWV was significantly decreased in the older male groups. Additionally, we also divided the female controls into a younger (< 60 years of age, n = 66) and an older (\geq 60 years of age, n = 8) groups, and the clinical and hemodynamic data of these two groups of subjects were showed in Table 3. It can be seen that the hPWV was significantly increased while the hPWV was significantly decreased in the older female groups. Therefore, age is indeed one of the major determinants of hPWV in healthy controls.

Table 4 shows the comparison between age-matched male healthy controls (n=23) and CABG patients (n=43). Though the body weight, BMI, SBP, DBP, PP and MAP were significantly higher in the male CABG patients, the hPWV in the male CABG patients were not significantly different from that of the male normal male controls. Similarly, Table 5 shows the comparison between age-matched female healthy controls (n=8) and CABG patients (n=4). Because most CABG patients in the veteran's hospital were male, the sample size of the female CABG

patients was small and there was no significant difference in hPWV and other hemodynamic data between those two female groups except HR.

Figure 3(a) and 3(b) showed the relationships between age and hPWV, and between body height and hPWV, in all healthy subjects (n=137), respectively. The hPWV decreases with increasing age, and increases with increasing body height.

Table 6 presents the results of the univariate analysis of the contributions of age, body height, SBP, DBP, MAP and PP to the changes in hPWV for all healthy subjects, male healthy subjects, female healthy subjects and male CABG subject. Again, the age was the strongest contributor to the change in hPWV in any group. The decrease in hPWV with age in all healthy subjects and CABG patients was - 0.033 and - 0.037 m/s per year, respectively. Body height was also an important contributor to the change in hPWV. However, the body height was not independent of age because body height correlated significantly with age ($r=-0.22$, $p=0.0084$ for all healthy subjects; $r=-0.34$, $p=0.023$ for male CABG, as shown in Figure 4(a) and 4(b)).

4. DISCUSSION

In the present study, the hPWV in 146 healthy subjects and 47 patients after coronary artery bypass graft (CABG) surgery were measured. We found that age was the strongest negative contributor to the change in hPWV for all healthy subjects ($p < 0.0001$), male healthy subjects ($p = 0.0007$), female healthy subjects ($p < 0.0001$) and male CABG subject ($p = 0.038$). That is, the older the subject is, the smaller hPWV the subject has. This result seems to be opposite to the observation of Vaitkevicius *et al.*²⁷ that the arteries become less elastic and the PWV, blood pressures and MAP become increased as people ages because the vasculature associated with ageing are caused by an increase in arterial wall thickness secondary to hyperplasia of the intima and by a loss of elastin in the media and its replacement with collagen. The discrepancy between our result and the result of Vaitkevicius *et al.*²⁷ might be that the arteries measured in this study were not the same as those in the study of Vaitkevicius *et al.* In the present study, the arteries measured at both hands are peripheral resistance vessels, whereas the arteries measured in the study of Vaitkevicius *et al.* are central large elastic arteries (e.g. aorta, carotid or femoral artery ...and so on). Since the arterial tree is not a homogenous system and there are major differences in the structure and

function of various arteries, it is likely that the PWV at both hands was different from that in the large arteries. Smulyan *et al.*⁴⁵ have reported a decrease in the brachial-radial pulse wave velocity with advancing age when transmural pressure was fixed at a selected value by enclosing the forearm in an airtight box. They attributed their results to differences in the wall properties of different parts of the arterial tree. Since the carotid-femoral pulse wave velocity is known to increase with ageing, it is highly probable that the PWV measured at the hand is different from that in the central large arteries. Furthermore, Boutouyrie *et al.*⁴⁶ have demonstrated that age had opposing effects on proximal and distal large arteries in normotensives and in hypertensives. This may be explained by the observation that radial arteries are rarely affected by the severe atherosclerosis that largely causes the stiffening seen in the central, more elastic arteries. This is consistent with our results that there were no significant difference in hPWV between male CABG patients and age-matched healthy men. Thus, arterial stiffness measured at different regions may have different roles in human.

Although the mechanisms by which the influence of various factors on arterial stiffness varies among different arterial regions are not fully understood, advanced glycation endproducts (AGE) deposited on aortic extracellular matrices⁴⁷ might be the possible mechanisms of arterial stiffening. Aortic AGE

content correlates with stiffness of human⁴⁸ and rat⁴⁷ aorta. The degree of aortic tissue glycation increases with age.⁴⁹ In animal experiments, age-related increase in aortic wall stiffness was prevented by treatment with aminoguanidine, an inhibitor of AGE formation.⁵⁰ Also, an AGE cross-link breaker reduced the stiffness of aorta but not systemic arterial resistance.⁵¹ On the other hand, Shige *et al.*⁵² found that cholesterol-lowering with simvastatin was associated with reduced PWV in the femoral-tibial region but not in the aorto-femoral segment. Because statins improve endothelium-dependent vasodilation,⁵³ stiffness of peripheral arteries might be more strongly controlled by the endothelium-dependent mechanism than that of central arteries. The results of these studies raise the possibility that AGE and endothelium-dependent mechanism might be involved in the preferential stiffening of the central (elastic) over peripheral (muscular) arteries as a result of ageing.

It is well established that the healthy endothelium plays an important role in modulating vascular tone via the tonic and numerous vasoactive substances, as well as in providing protection from the development of thrombosis and atherosclerotic vascular disease.⁵⁴ Accumulating evidence indicates that ageing is an independent risk factor for the development of atherosclerosis and is associated with a progressive decline in endothelium-dependent vasodilatation in

resistance and conduit vessels.^{55;56} Indeed, reduced blood flow and lower vascular conductance have been reported in some regional circulations with adult ageing.⁵⁷ Reduced blood flow capacity may be related to decline in the maximal vasodilatory capacity of the resistance vessels. Dinunno *et al.*⁵⁸⁻⁶¹ have demonstrated that the age-related reductions in basal limb blood flow and vascular conductance are mediated largely by chronically elevated sympathetic α -adrenergic vasoconstriction. Additionally, Muller-Delp *et al.*⁶² have demonstrated that ageing impairs vasodilatory responses mediated through the endothelium of resistance arterioles from locomotory muscle, whereas smooth muscle vasodilatory responses remain intact with ageing. Hence, ageing is associated with the changes in the function of blood vessels, such as endothelial dysfunction, reductions in basal limb blood flow, and reduced vascular conductance. The above-mentioned observations might account for our finding that ageing is related to reduced hPWV in both healthy subjects and patients after CABG. Further studies are needed to clarify the relationships between reduced hPWV with ageing and age-related endothelial dysfunction or age-related reductions in basal limb blood flow and vascular conductance.

Several recent studies have shown that there is sex-related difference in PWV in different regions. For instances, London *et al.*⁶³ reported that both

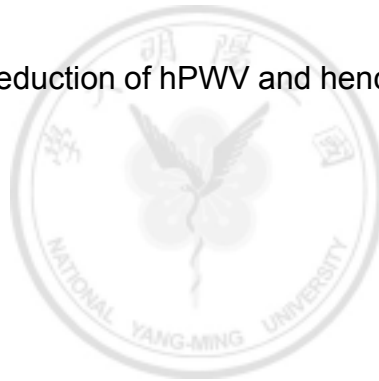
carotid-radial PWV and femoral-tibial PWV in premenopausal women were lower than in age-matched men. Tomiyama *et al.*⁶⁴ have also demonstrated that the heart-brachial PWV, which assesses peripheral arterial stiffness in the upper limb in the arterial tree, was higher in males than in age-matched female. In addition, no difference was found in aortic PWV^{65;66} or carotid artery augmentation index⁶⁶ (one of the index used to assess arterial stiffness) between postmenopausal women with and without hormone replacement therapy. Similarly, we found that male sex was a significant and independent factor associated with increased hPWV. All these studies suggested that sex-related difference in arterial stiffness occurred preferentially in the peripheral rather than in the central arteries.

The reason for this difference in PWV for different genders is not clear. One reason might be that the smooth muscle tone and vessel wall structure (elastin/collagen) could be influenced by sex hormones. Previous studies have demonstrated that estrogen increases blood flow through both endothelium-dependent⁶⁷ and endothelium-independent mechanisms,⁶⁸ but the effect of progesterone on vascular tone is more varied and controversial.⁶⁹ These studies suggest that estrogen may play a more important role than progesterone in the reduction of arterial stiffness in females. Additionally, estrogen has other well-documented antiatherogenic effects that can reduce arterial stiffness

including inhibition of smooth muscle cell proliferation⁷⁰ and modulation of extracellular matrix composition^{71;72}. Finally, estrogen is well known to improve lipoproteins and lower fibrinogen levels.⁷³ In contrast to female hormones, male sex steroids appear to have more widespread actions that promote vessel stiffening in both central and peripheral regions. Androgen receptors have been identified in vascular tissues in experimental animals and cell culture⁷⁴⁻⁷⁷ but are less well studied than female sex steroid receptors. There are no reports with regard to androgen receptor localization in human vascular tissues. Androgen deprivation has, however, been shown to enhance endothelium-dependent vasodilation in adult men.⁷⁸ An elevation in androgen levels would thus increase arterial tone and may contribute to stiffening in the vessels. Androgens also increase smooth muscle cell proliferation⁷⁹ and monocyte adhesion to endothelial cells⁸⁰, atherogenic effects that also promote arterial stiffening. All these studies suggest that estrogen might play an important role in the reduction of arterial stiffness in females, while androgen might contribute to the stiffening of the blood vessels.

In the present study, although body height was also an important contributor to the change in hPWV, the body height was not independent of age because body height correlated significantly and negatively with age ($r = -0.22$, $p = 0.0084$)

for all healthy subjects; $r = -0.34$, $p = 0.023$ for male CABG patients). Actually, some Investigators have reported that an inverse relationship exists between the augmentation index (one of the index used to assess arterial stiffness) and body height.^{81;82} This is assumed to be due to the shorter distance from the origin of the waveform to the point of reflection, leading to a quicker return of the reflected wave for a given PWV. Short body height is known to be a risk factor for cardiovascular disease.⁸³ Hence, it has been suggested that body height should be controlled in the analysis of results.^{84;85} Our results suggested that body height might play its role in the reduction of hPWV and hence arterial stiffness through its relation with age.



5. CONCLUSION

The present study showed that age is the dominant factor contributing negatively to hPWV in healthy subjects and patients after CABG, and that male sex is a significant and independent factor associated with increased hPWV in healthy subjects. There is no difference in hPWV between healthy subjects and patients after CABG. Further studies are needed to elucidate the mechanisms and clinical implications of hPWV in health and diseases.



REFERENCES

1. 福州人民醫院校釋。《脈經校釋》。北京：人民衛生出版社。1984，頁 7。
2. 王強。中醫脈診現代化研究的困境與對策。河南中醫 1994；14:頁 139。
3. 劉文娜。八維脈像與血流動力學的相關性研究 (碩士論文)。北京：北京中醫藥大學，2002。
4. 馮曄。周學海位數形勢學說應用於脈學理論與實驗之研究--以脈位浮變之研究為例 (碩士論文)。私立中國醫藥學院中國醫學研究所，1997，頁 2。
5. 劉晉平。數據挖掘在中醫脈診研究中的應用 (碩士論文)。天津：天津中醫學院，2002 頁，頁 92。
6. 費兆馥。現代中醫脈診學。北京：人民衛生出版社。2003。
7. 熊鑒然。弦脈與血流動力學關係的實驗研究。中西醫結合雜誌，1982，2(3):172。 .
1982.
8. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension 1999;33:1111-17.
9. Oliver JJ, Webb DJ. Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. Arterioscler Thromb Vasc Biol 2003;23:554-66.

10. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. *Circulation* 2001;103:987-92.
11. O'Rourke MF, Mancia G. Arterial stiffness. *J Hypertens* 17(1):1-4, 1999.
12. Avolio A, Jones D, Tafazzoli-Shadpour M. Quantification of alterations in structure and function of elastin in the arterial media. *Hypertension* 1998;32:170-75.
13. Kinlay S, Creager MA, Fukumoto M, Hikita H, Fang JC, Selwyn AP et al. Endothelium-derived nitric oxide regulates arterial elasticity in human arteries In vivo. *Hypertension* 2001;38:1049-53.
14. Wilkinson IB, Qasem A, McEniery CM, Webb DJ, Avolio AP, Cockcroft JR. Nitric oxide regulates local arterial distensibility in vivo. *Circulation* 2002;105:213-17.
15. Bank AJ, Wang H, Holte JE, Mullen K, Shammass R, Kubo SH. Contribution of collagen, elastin, and smooth muscle to in vivo human brachial artery wall stress and elastic modulus. *Circulation* 1996;94:3263-70.
16. Bank AJ, Kaiser DR, Rajala S, Cheng A. In vivo human brachial artery elastic

mechanics : effects of smooth muscle relaxation. *Circulation* 1999;100:41-47.

17. Medley TL, Cole TJ, Gatzka CD, Wang WYS, Dart AM, Kingwell BA. Fibrillin-1 genotype is associated with aortic stiffness and disease severity in patients with coronary artery disease. *Circulation* 2002;105:810-15.

18. Lajemi M, Labat C, Gautier S, Lacolley P, Safar M, Asmar R et al. Angiotensin II type 1 receptor-153A/G and 1166A/C gene polymorphisms and increase in aortic stiffness with age in hypertensive subjects. *J Hypertens* 2001;19:407-13.

19. Lajemi M, Gautier S, Poirier O, Baguet JP, Mimran A, Gosse P et al. Endothelin gene variants and aortic and cardiac structure in never-treated hypertensives. *Am J Hypertens* 2001;14:755-60.

20. Balkestein EJ, Staessen JA, Wang JG, van der Heijden-Spek J, Van Bortel LM, Barlassina C et al. Carotid and femoral artery stiffness in relation to three candidate genes in a white population. *Hypertension* 2001;38:1190-97.

21. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM et al. Assessment of arterial distensibility by automatic pulse wave velocity measurement : validation and clinical application studies. *Hypertension* 1995;26:485-90.

22. Sutton-Tyrrell K, Mackey RH, Holubkov R, Vaitkevicius PV, Spurgeon HA, Lakatta EG. Measurement variation of aortic pulse wave velocity in the elderly. *Am J Hypertens* 2001;14:463-68.
23. Wilkinson IB, Fuchs SA, Jansen IM, Spratt JC, Murray GD, Cockcroft JR et al. Reproducibility of pulse wave velocity and augmentation index measured by pulse wave analysis. *J Hypertens* 1998;16:2079-84.
24. Mohiaddin RH, Firmin DN, Longmore DB. Age-related changes of human aortic flow wave velocity measured noninvasively by magnetic resonance imaging. *J Appl Physiol* 1993;74:492-97.
25. Lantelme P, Mestre C, Lievre M, Gressard A, Milon H. Heart rate: an important confounder of pulse wave velocity assessment. *Hypertension* 2002;39:1083-87.
26. Lehmann ED, Hopkins KD, Rawesh A, Joseph RC, Kongola K, Coppack SW et al. Relation between number of cardiovascular risk factors/events and noninvasive doppler ultrasound assessments of aortic compliance. *Hypertension* 1998;32:565-69.
27. Vaitkevicius PV, Fleg JL, Engel JH, O'Connor FC, Wright JG, Lakatta LE et al. Effects of age and aerobic capacity on arterial stiffness in healthy adults.

Circulation 1993;88:1456-62.

28. Lahmann ED, Watts GF, Gosling RG. Aortic distensibility and

hypercholesterolaemia. Lancet 1992;340:1171-72.

29. Lehmann ED, Gosling RG, Sonksen PH. Arterial wall compliance in diabetes.

Diabet.Med 1992;9:114-19.

30. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L et al. Aortic

stiffness is an independent predictor of all-cause and cardiovascular mortality

in hypertensive patients. Hypertension 2001;37:1236-41.

31. Boutouyrie P, Tropeano AI, Asmar R, Gautier I, Benetos A, Lacolley P et al.

Aortic stiffness is an independent predictor of primary coronary events in

hypertensive patients: a longitudinal study. Hypertension 2002;39:10-15.

32. Benetos A, Adamopoulos C, Bureau JM, Temmar M, Labat C, Bean K et al.

Determinants of accelerated progression of arterial stiffness in normotensive

subjects and in treated hypertensive subjects over a 6-year period. Circulation

2002;105:1202-07.

33. Blacher J, Guerin AP, Pannier B, Marchais SJ, Safar ME, London GM. Impact

of aortic stiffness on survival in end-stage renal disease. Circulation

1999;99:2434-39.

34. Safar ME, Blacher J, Pannier B, Guerin AP, Marchais SJ, Guyonvarc'h PM et al. Central pulse pressure and mortality in end-stage renal disease. *Hypertension* 2002;39:735-38.
35. Meaume S, Benetos A, Henry OF, Rudnichi A, Safar ME. Aortic pulse wave velocity predicts cardiovascular mortality in subjects >70 years of age. *Arterioscler Thromb Vasc Biol* 2001;21:2046-50.
36. Shoji T, Emoto M, Shinohara K, Kakiya R, Tsujimoto Y, Kishimoto H et al. Diabetes mellitus, aortic stiffness, and cardiovascular mortality in end-stage renal disease. *J Am Soc Nephrol* 2001;12:2117-24.
37. Taniwaki H, Shoji T, Emoto M, Kawagishi T, Ishimura E, Inaba M et al. Femoral artery wall thickness and stiffness in evaluation of peripheral vascular disease in type 2 diabetes mellitus. *Atherosclerosis* 2001;158:207-14.
38. Suzuki E, Kashiwagi A, Nishio Y, Egawa K, Shimizu S, Maegawa H et al. Increased arterial wall stiffness limits flow volume in the lower extremities in type 2 diabetic patients. *Diabetes Care* 2001;24:2107-14.
39. Taniwaki H, Kawagishi T, Emoto M, Shoji T, Kanda H, Maekawa K et al. Correlation between the intima-media thickness of the carotid artery and aortic pulse-wave velocity in patients with type 2 diabetes. *Vessel wall properties in*

type 2 diabetes. *Diabetes Care* 1999;22:1851-57.

40. Emoto M, Nishizawa Y, Kawagishi T, Maekawa K, Hiura Y, Kanda H et al.

Stiffness indexes beta of the common carotid and femoral arteries are associated with insulin resistance in NIDDM. *Diabetes Care* 1998;21:1178-82.

41. Megnien JL, Simon A, Valensi P, Flaud P, Merli I, Levenson J. Comparative

effects of diabetes mellitus and hypertension on physical properties of human large arteries. *J Am Coll Cardiol* 1992;20:1562-68.

42. Lo CS, Relf IR, Myers KA, Wahlqvist ML. Doppler ultrasound recognition of

preclinical changes in arterial wall in diabetic subjects: compliance and pulse-wave damping. *Diabetes Care* 1986;9:27-31.

43. Avolio AP, Chen SG, Wang RP, Zhang CL, Li MF, O'Rourke MF. Effects of

aging on changing arterial compliance and left ventricular load in a northern Chinese urban community. *Circulation* 1983;68:50-58.

44. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex

on arterial hemodynamics and blood pressure : role of body height. *Hypertension* 1995;26:514-19.

45. Smulyan H, Csermely TJ, Mookherjee S, Warner RA. Effect of age on arterial

distensibility in asymptomatic humans. *Arteriosclerosis* 1983;3:199-205.

46. Boutouyrie P, Laurent S, Benetos A, Girerd XJ, Hoeks AP, Safar ME. Opposing effects of ageing on distal and proximal large arteries in hypertensives. *J Hypertens Suppl.* 1992;10:S87-S91.
47. Bruel A, Oxlund H. Changes in biomechanical properties, composition of collagen and elastin, and advanced glycation endproducts of the rat aorta in relation to age. *Atherosclerosis* 1996;127:155-65.
48. Sims TJ, Rasmussen LM, Oxlund H, Bailey AJ. The role of glycation cross-links in diabetic vascular stiffening. *Diabetologia* 1996;39:946-51.
49. Oimomi M, Igaki N, Hata F, Kitamura Y, Nishimoto S, Baba S et al. Age- and diabetes-accelerated glycation in the human aorta. *Arch Gerontol Geriatr* 1989;8:123-27.
50. Cantini C, Kieffer P, Corman B, Liminana P, Atkinson J, Lartaud-Idjouadiene I. Aminoguanidine and aortic wall mechanics, structure, and composition in aged rats. *Hypertension* 2001;38:943-48.
51. Kass DA, Shapiro EP, Kawaguchi M, Capriotti AR, Scuteri A, deGroof RC et al. Improved arterial compliance by a novel advanced glycation end-product crosslink breaker. *Circulation* 2001;104:1464-70.

52. Shige H, Dart A, Nestel P. Simvastatin improves arterial compliance in the lower limb but not in the aorta. *Atherosclerosis* 2001;155:245-50.
53. Koh KK, Cardillo C, Bui MN, Hathaway L, Csako G, Waclawiw MA et al. Vascular effects of estrogen and cholesterol-lowering therapies in hypercholesterolemic postmenopausal women. *Circulation* 1999;99:354-60.
54. Rubanyi GM. The role of endothelium in cardiovascular homeostasis and diseases. *J Cardiovasc Pharmacol* 1993;22 Suppl 4:S1-14.
55. Egashira K, Inou T, Hirooka Y, Kai H, Sugimachi M, Suzuki S et al. Effects of age on endothelium-dependent vasodilation of resistance coronary artery by acetylcholine in humans. *Circulation* 1993;88:77-81.
56. Baumbach GL, Dobrin PB, Hart MN, Heistad DD. Mechanics of cerebral arterioles in hypertensive rats. *Circ Res* 1988;62:56-64.
57. Leithe ME, Hermiller JB, Magorien RD, Unverferth DV, Leier CV. The effect of age on central and regional hemodynamics. *Gerontology* 1984;30:240-46.
58. Dinunno FA, Jones PP, Seals DR, Tanaka H. Age-associated arterial wall thickening is related to elevations in sympathetic activity in healthy humans. *Am J Physiol Heart Circ Physiol* 2000;278:H1205-H1210.

59. Dinunno FA, Seals DR, DeSouza CA, Tanaka H. Age-related decreases in basal limb blood flow in humans: time course, determinants and habitual exercise effects. *J Physiol* 2001;531:573-79.
60. Dinunno FA, Jones PP, Seals DR, Tanaka H. Limb blood flow and vascular conductance are reduced with age in healthy humans: relation to elevations in sympathetic nerve activity and declines in oxygen demand. *Circulation* 1999;100:164-70.
61. Dinunno FA, Tanaka H, Stauffer BL, Seals DR. Reductions in basal limb blood flow and vascular conductance with human ageing: role for augmented alpha-adrenergic vasoconstriction. *J Physiol* 2001;536:977-83.
62. Muller-Delp JM, Spier SA, Ramsey MW, Delp MD. Aging impairs endothelium-dependent vasodilation in rat skeletal muscle arterioles. *Am J Physiol Heart Circ Physiol* 2002;283:H1662-H1672.
63. London GM, Guerin AP, Pannier B, Marchais SJ, Stimpel M. Influence of sex on arterial hemodynamics and blood pressure : role of body height. *Hypertension* 1995;26:514-19.
64. Tomiyama H, Yamashina A, Arai T, Hirose K, Koji Y, Chikamori T et al. Influences of age and gender on results of noninvasive brachial-ankle pulse

wave velocity measurement--a survey of 12517 subjects. *Atherosclerosis* 2003;166:303-09.

65. Lehmann ED, Hopkins KD, Parker JR, Turay RC, Rymer J, Fogelman I et al.

Aortic distensibility in post-menopausal women receiving Tibolone. *Br J*

Radiol 1994;67:701-05.

66. Tanaka H, DeSouza CA, Seals DR. Arterial stiffness and hormone

replacement use in healthy postmenopausal women. *J Gerontol Ser A-Biol Sci*

Med Sci 1998;53:M344-M346.

67. Caulin-Glaser T, Garcia-Cardena G, Sarrel P, Sessa WC, Bender JR. 17

-estradiol regulation of human endothelial cell basal nitric oxide release,

independent of cytosolic Ca²⁺ mobilization. *Circ Res* 1997;81:885-92.

68. Collins P, Beale CM, Rosano GM. Oestrogen as a calcium channel blocker.

Eur Heart J 1996;17 Suppl D:27-31.

69. Thompson J, Khalil RA. Gender differences in the regulation of vascular tone.

Clin Exp Pharmacol Physiol 2003;30:1-15.

70. Vargas R, Wroblewska B, Rego A, Hatch J, Ramwell PW. Oestradiol inhibits

smooth muscle cell proliferation of pig coronary artery. *Br J Pharmacol*

1993;109:612-17.

71. Cox RH, Fischer GM. Effects of sex hormones on the passive mechanical properties of rat carotid artery. *Blood Vessels* 1978;15:266-76.
72. Fischer GM, Swain ML. Effect of sex hormones on blood pressure and vascular connective tissue in castrated and noncastrated male rats. *Am J Physiol* 1977;232:H617-H621.
73. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. *JAMA* 1995;273:199-208.
74. Lin AL, McGill HC, Jr., Shain SA. Hormone receptors of the baboon cardiovascular system. Biochemical characterization of aortic cytoplasmic androgen receptors. *Arterioscler Thromb Vasc Biol* 1981;1:257-64.
75. Tamaya T, Wada K, Nakagawa M, Misao R, Itoh T, Imai A et al. Sexual dimorphism of binding sites of testosterone and dihydrotestosterone in rabbit model. *Comp Biochem Physiol Comp Physiol* 1993;105:745-49.
76. Higashiura K, Mathur RS, Halushka PV. Gender-related differences in androgen regulation of thromboxane A2 receptors in rat aortic smooth-muscle cells. *J Cardiovasc Pharmacol* 1997;29:311-15.

77. Ba ZF, Wang P, Koo DJ, Ornan DA, Bland KI, Chaudry IH. Attenuation of vascular endothelial dysfunction by testosterone receptor blockade after trauma and hemorrhagic shock. *Arch Surg* 2001;136:1158-63.
78. Herman SM, Robinson JTC, McCredie RJ, Adams MR, Boyer MJ, Celermajer DS. Androgen deprivation is associated with enhanced endothelium-dependent dilatation in adult men. *Arterioscler Thromb Vasc Biol* 1997;17:2004-09.
79. Fujimoto R, Morimoto I, Morita E, Sugimoto H, Ito Y, Eto S. Androgen receptors, 5 alpha-reductase activity and androgen-dependent proliferation of vascular smooth muscle cells. *J Steroid Biochem Mol Biol* 1994;50:169-74.
80. McCrohon JA, Jessup W, Handelsman DJ, Celermajer DS. Androgen exposure increases human monocyte adhesion to vascular endothelium and endothelial cell expression of vascular cell adhesion molecule-1. *Circulation* 1999;99:2317-22.
81. Yasmin, Brown MJ. Similarities and differences between augmentation index and pulse wave velocity in the assessment of arterial stiffness. *QJM* 1999;92:595-600.
82. Kelly RP, Millasseau SC, Ritter JM, Chowienczyk PJ. Vasoactive drugs

influence aortic augmentation index independently of pulse-wave velocity in healthy men. Hypertension 2001;37:1429-33.

83. O'Rourke MF, Pauca A, Jiang XJ. Pulse wave analysis. Br J Clin Pharmacol 2001;51:507-22.

84. Kannam JP, Levy D, Larson M, Wilson PWF. Coronary heart disease/myocardial infarction: short stature and risk for mortality and cardiovascular disease events: The Framingham Heart Study. Circulation 1994;90:2241-47.

85. Smulyan H, Marchais SJ, Pannier B, Guerin AP, Safar ME, London GM. Influence of body height on pulsatile arterial hemodynamic data. J Am Coll Cardiol 1998;31:1103-09.

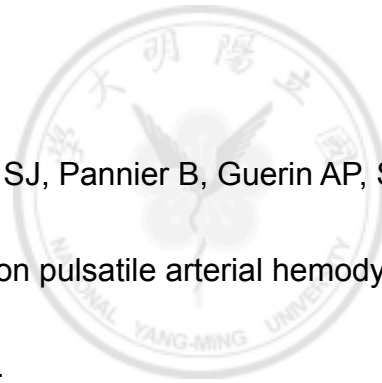


TABLE 1. Clinical and hemodynamic data of male and female healthy controls

Variables	Men (n=63)	Women (n=74)	p value
Age (yr)	43.7±14.8	43.5±13.1	NS
Body height (cm)	168.8±5.9	157.7±5.7	< 0.001
Body weight (kg)	67.2±10.8	54.1±7.5	< 0.001
BMI (kg/m ²)	23.5±3.1	21.8±3.0	< 0.001
SBP (mmHg)	118.8±11.3	112.6±12.1	0.002
DBP (mmHg)	75.2±9.4	73.9±9.7	NS
PP (mmHg)	43.6±7.8	38.8±5.8	< 0.001
MAP (mmHg)	89.7±9.4	86.8±10.2	NS
HR (bpm)	73.0±10.0	73.4±8.7	NS
hPWV (m/s)	5.00±0.99	4.30±0.97	< 0.001

Data are means±SD; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HR: heart rate; hPWV: pulse wave velocity measured at both hands; NS: not significant.

TABLE 2. Clinical and hemodynamic data of younger and older male healthy subjects

Variable	Younger men (n=49)	Older men (n=23)	p value
Age (yr)	39.4±16.7	72.7±16.5	< 0.001
Body height (cm)	169.0±5.6	166.1±7.7	NS
Body weight (kg)	66.3±8.8	63.2±9.3	NS
BMI (kg/m ²)	23.2±2.5	22.8±2.4	NS
SBP (mmHg)	116.7±10.3	126.0±11.2	< 0.001
DBP (mmHg)	73.4±8.8	76.4±8.2	NS
PP (mmHg)	43.2±8.2	49.6±7.2	0.002
MAP (mmHg)	87.8±8.5	92.9±8.7	0.022
HR (bpm)	72.9±9.7	73.9±12.2	NS
hPWV (m/s)	5.09±0.97	4.17±0.69	< 0.001

Data are means±SD; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HR: heart rate; hPWV: pulse wave velocity measured at both hands; NS: not significant.

TABLE 3. Clinical and hemodynamic data of younger and older female healthy subjects

Variable	Younger women (n=66)	Older women (n=8)	p value
Age (yr)	41.1±11.8	63.3±1.6	< 0.001
Body height (cm)	158.1±5.5	155.1±6.5	NS
Body weight (kg)	54.1±7.4	53.6±8.8	NS
BMI (kg/m ²)	21.7±3.0	22.2±3.0	NS
SBP (mmHg)	112.4±12.5	114.9±9.2	NS
DBP (mmHg)	74.0±9.9	73.0±8.0	NS
PP (mmHg)	38.4±5.6	41.9±6.9	NS
MAP (mmHg)	86.8±10.5	87.0±7.7	NS
HR (bpm)	74.0±8.4	68.6±9.8	NS
hPWV (m/s)	4.41±0.95	3.31±0.45	0.001

Data are means±SD; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HR: heart rate; hPWV: pulse wave velocity measured at both hands; NS: not significant.

TABLE 4. Clinical and hemodynamic data of male controls and male CABG patients

Variable	Male Controls (n=23)	Male CABG (n=43)	p value
Age (yr)	72.7±6.5	71.3±8.3	NS
Body height (cm)	166.3±7.7	166.0±7.8	NS
Body weight (kg)	63.2±9.3	68.9±9.2	0.021
BMI (kg/m ²)	22.8±2.4	25.0±2.6	0.002
SBP (mmHg)	126.0±11.2	140.8±18.6	0.003
DBP (mmHg)	76.4±8.2	82.1±11.4	0.037
PP (mmHg)	49.6±7.2	58.7±14.1	0.012
MAP (mmHg)	92.9±8.7	101.7±12.6	0.009
HR (bpm)	73.9±12.2	72.1±9.5	NS
hPWV (m/s)	4.17±0.69	4.11±1.03	NS

Data are means±SD; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HR: heart rate; hPWV: pulse wave velocity measured at both hands; NS: not significant.

TABLE 5. Clinical and hemodynamic data of female controls and female CABG patients

Variable	Female CNTL (n=8)	Female CABG (n=4)	p value
Age (yr)	63.3±1.6	65.3±11.5	NS
Body height (cm)	155.1±6.5	154.0±4.2	NS
Body weight (kg)	53.6±8.8	57.4±8.5	NS
BMI (kg/m ²)	22.2±3.0	24.3±3.9	NS
SBP (mmHg)	114.9±9.2	131.0±20.7	NS
DBP (mmHg)	73.0±8.0	83.8±13.6	NS
PP (mmHg)	41.9±6.9	47.3±8.5	NS
MAP (mmHg)	87.0±7.7	99.5±15.8	NS
HR (bpm)	68.6±9.8	80.5±3.9	0.045
hPWV (m/s)	3.31±0.45	3.70±1.24	NS

Data are means±SD; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; PP: pulse pressure; MAP: mean arterial pressure; HR: heart rate; hPWV: pulse wave velocity measured at both hands; NS: not significant.

TABLE 6. The change in hPWV with age, SBP, DBP, PP, MAP or body height
(univariate linear regression analysis)

Correlation	Slope	R value	p value
Men (n=63)			
Age (yr)	-0.027	-0.42	0.0007
SBP (mmHg)	-0.025	-0.29	0.019
DBP (mmHg)	-0.032	-0.33	0.008
MAP (mmHg)	-0.033	-0.34	0.007
Women (n=74)			
Age (yr)	-0.037	-0.57	< 0.0001
SBP (mmHg)	-0.017	-0.23	0.048
PP (mmHg)	-0.038	-0.27	0.018
Total (n=137)			
Age (yr)	-0.033	-0.47	< 0.0001
Body height (cm)	0.039	0.33	< 0.0001
Male CABG (n=43)			
Age (yr)	-0.037	-0.32	0.038
Body height (cm)	0.029	0.32	0.039

Data are means±SD; SBP: systolic blood pressure; DBP: diastolic blood pressure;
PP: pulse pressure; MAP: mean arterial pressure;

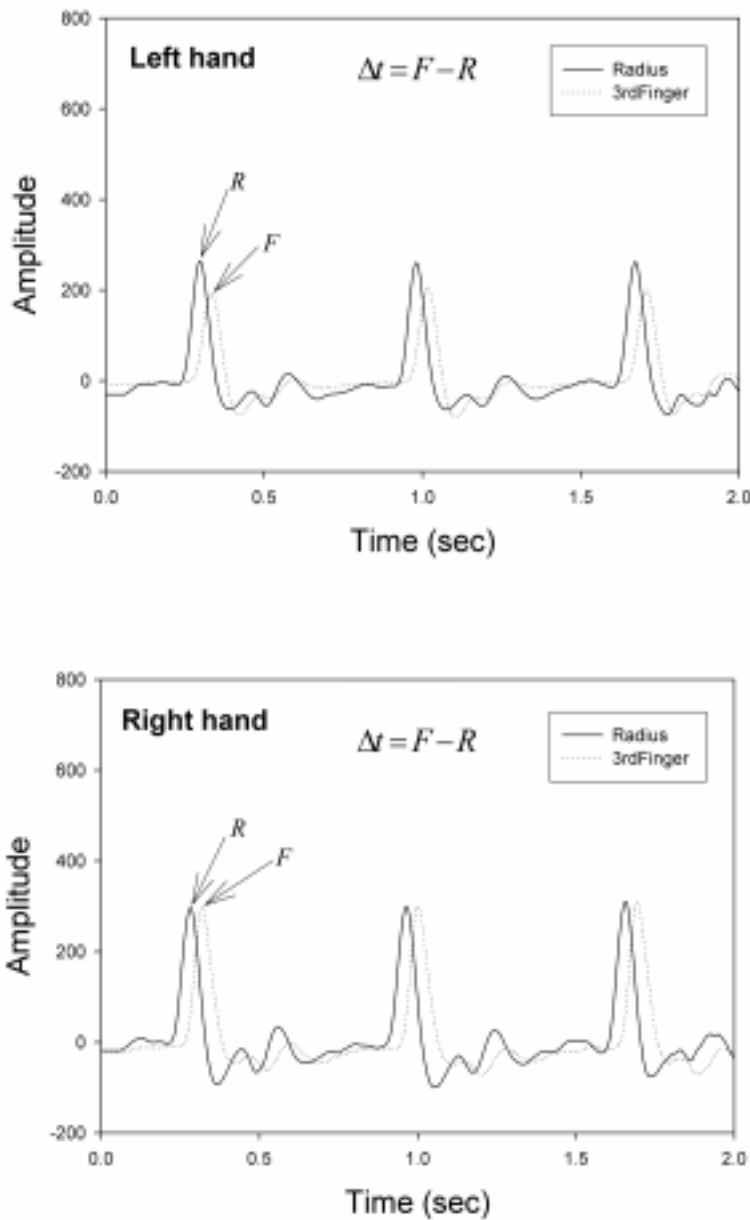


FIGURE 1. The distance Δx from the styloid process of the radius to the mid-portion of the 1st phalanx of the 3rd finger were measured, and the time interval Δt between the peak of the pulse wave detected at the styloid process of the radius and the peak of the pulse wave detected at the mid-portion of the 1st phalanx of the 3rd finger was measured. The hPWV was calculated using the formula: $hPWV = \Delta x / \Delta t$.

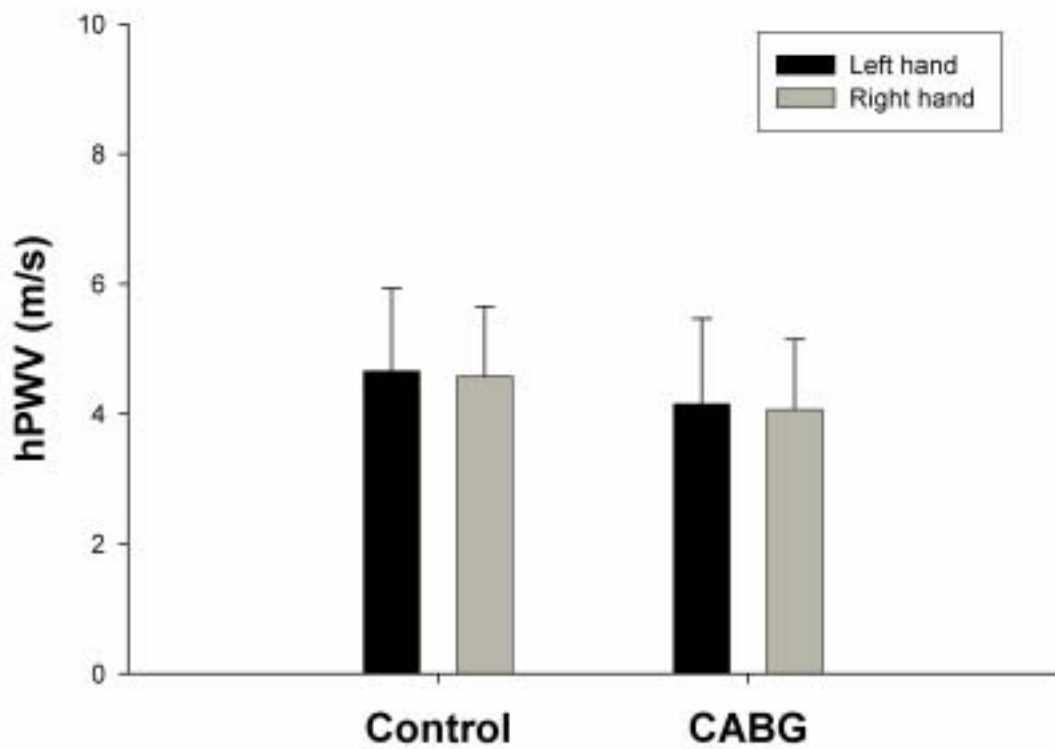


FIGURE 2. The hPWV measured at left and right hands in the control group and CABG group. There is no difference in left and right hPWV in either group.

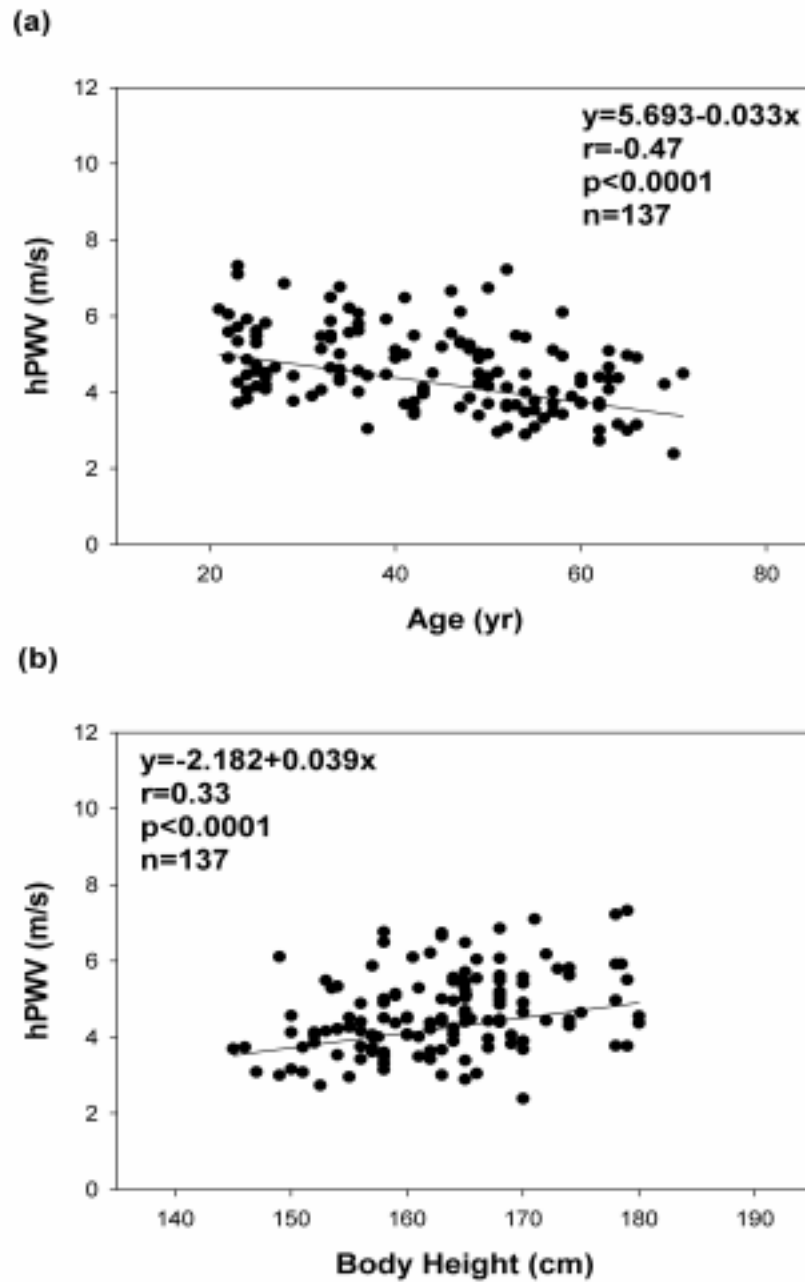


FIGURE 3 (a). Relationships between subject age and hPWV in healthy controls. The hPWV decreases with increasing age. (b). Relationships between subject height and hPWV. The hPWV increases with increasing body height.

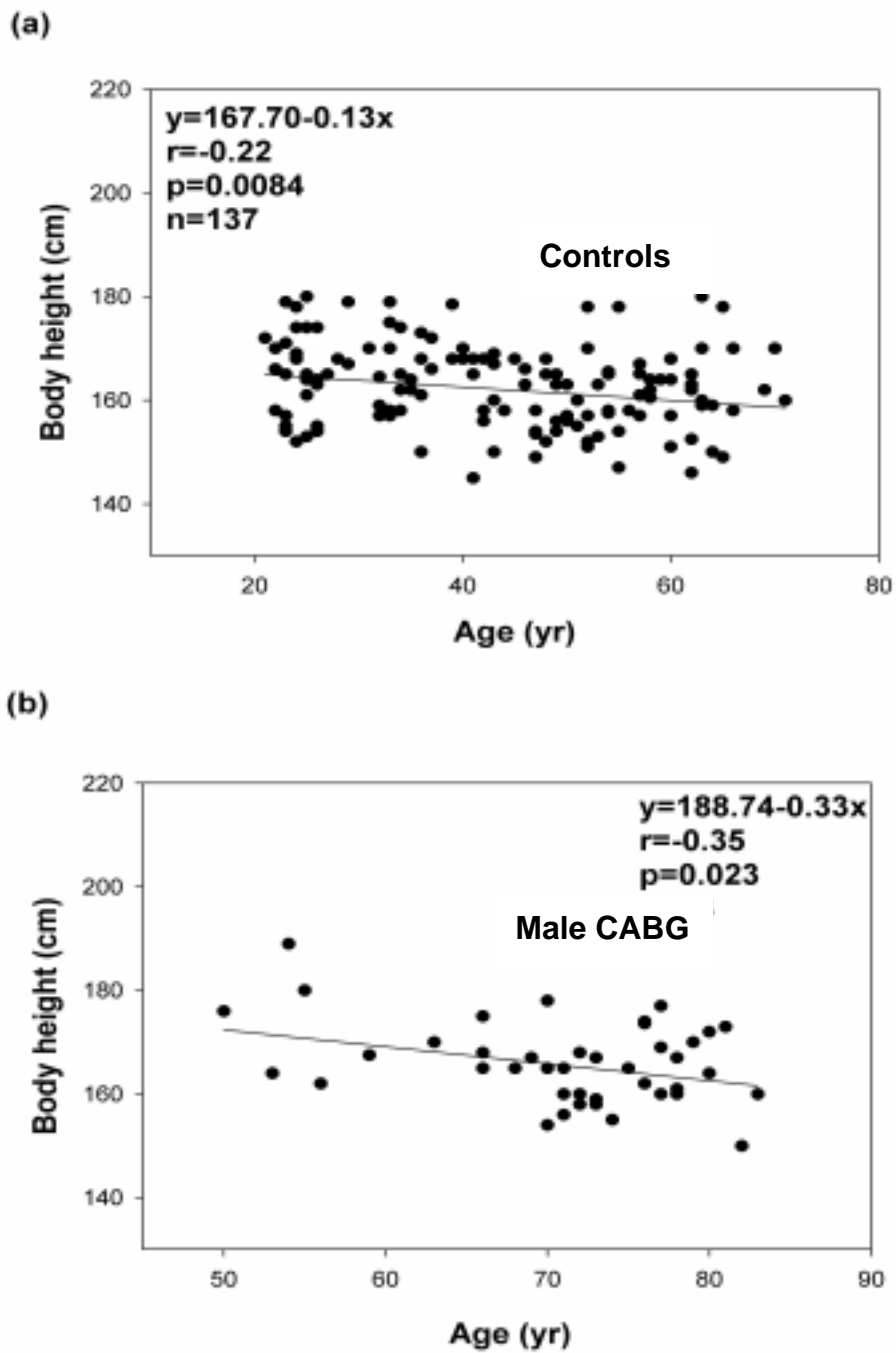


FIGURE 4. Relationships between subject age and body height in healthy controls and male CABG patients. The body height decreases with increasing age (a) for all healthy subjects, and (b) for male CABG patients.