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Vztah mezi vlastnostmi tepen dolních končetin a aortální tuhostí a jejich vliv na kardiovaskulární riziko

The relationship between lower extremity arterial properties and aortic stiffness and their effect on cardiovascular risk

Typ závěrečné práce - disertační

Vedoucí závěrečné práce/Školitel: Prof. MUDr. Renata Cífková, CSc.

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Použité zkratky

ABI poměr kotník-paže (ankle-brachial index)

AGE pokročilé konečné produkty glykace (advanced glycation end products)

aPWV rychlost šíření pulzové vlny na aortě (aortic pulse wave velocity)

baPWV rychlost šíření pulzové vlny mezi paží a kotníkem (brachial-ankle PWV)

C poddajnost (compliance)

CAVI cévní index srdce-kotník (cardio-ankle vascular index)

caPWV rychlost šíření pulzové vlny mezi krční tepnou a kotníkem

cfPWV rychlost šíření pulzové vlny mezi karotickou a femorální tepnou

CO srdeční výdej (cardiac output)

CKD chronické onemocnění ledvin (chronic kidney disease)

D roztažnost (distensibility)

DTK diastolický krevní tlak

ICHDK ischemická choroba dolních končetin

LK levá komora

MAP střední arteriální tlak (mean arterial pressure)

MMP matrix metaloproteináza

NO oxid dusnatý

PP pulzní tlak (pulse pressure)

PR periferní rezistence

PWV rychlost šíření pulzové vlny (pulse wave velocity)

STK systolický krevní tlak

σ povrchové napětí (stress)

ε strain

Obsah

Abstrakt

Poměr systolického tlaku na kotníku k systolickému tlaku na paži (poměr kotník-paže - ABI) je využíván v diagnostice ischemické choroby dolních končetin. Jeho snížená hodnota je známkou obstrukce lumina tepny, zatímco abnormálně zvýšená hodnota je způsobena inkompresibilitou tepen dolních končetin. Zatímco zvýšená tuhost aorty, měřená jako rychlost pulzové vlny mezi karotickou a femorální tepnou, je schopna predikovat kardiovaskulární riziko, zvýšená tuhost tepen dolních končetin, měřená jako rychlost pulzové vlny, nemá nezávislou prediktivní hodnotu. Přesto je inkompresibilita tepen dolních končetin stanovená pomocí ABI v nezávislém vztahu se zvýšeným kardiovaskulárním rizikem. Cílem naší práce bylo zjistit vztah mezi vlastnostmi tepen dolních končetin a aortální tuhostí a jejich vliv na kardiovaskulární riziko. Zjistili jsme, že výsledky oscilometrické a dopplerovské metody měření ABI nelze zaměňovat, protože oscilometrická metoda systematicky nadhodnocuje nízké hodnoty ABI a podhodnocuje vysoké hodnoty ABI. Proto je pro diagnostiku inkompresibility tepen dolních končetin vhodnější dopplerovská metoda měření ABI. Dále jsme ukázali, že věk a kardiovaskulární rizikové faktory mají menší vliv na tuhost tepen dolních končetin než na tuhost aorty. V naší studii zvýšený ABI jako projev inkompresibility tepen dolních končetin nebyl ve vztahu pouze se zvýšenou tuhostí tepen dolních končetin, ale i se zvýšenou tuhostí aorty. To znamená, že jedním z mechanizmů zvýšeného kardiovaskulárního rizika osob s inkompresibilitou tepen dolních končetin může být zvýšená tuhost aorty, která prostřednictvím zvýšené impedance aorty zvyšuje systolický tlak v aortě, což vede ke zvýšení afterloadu levé komory a rozvoji hypertrofie. Intervence zaměřené na snížení aortální tuhosti u osob s vysokým ABI by mohly snížit jejich kardiovaskulární riziko.

Abstract

The ratio of systolic blood pressure at the ankle to arm systolic pressure (ankle-brachial index - ABI) is used in the diagnosis of peripheral vascular disease. While its reduced value suggests obstruction of the arterial lumen, an abnormally elevated value is due to incompressibility of lower extremity arteries. While increased stiffness of the aorta, measured as carotid-femoral pulse wave velocity, is able to predict cardiovascular risk, increased pulse wave velocity of the leg arteries has no independent predictive value. Despite that, incompressibility of lower extremity arteries, diagnosed using ABI measurement, is independently associated with increased cardiovascular risk. The aim of our study was to determine the relationship between the characteristics of lower limb arteries and aortic stiffness, and their impact on cardiovascular risk. Our study showed that the results of oscillometric and Doppler ABI measurement methods are not interchangeable, because the oscillometric method systematically overestimates low values and underestimates high ABI values. Therefore, the diagnosis of lower limb arteries incompressibility should be based on the Doppler method of ABI measurement. Furthermore, we showed that age and cardiovascular risk factors have only a small effect on lower extremity arteries, but a major effect on aortic stiffness. In our study, increased ABI as a sign of lower extremity arteries incompressibility, was associated not only with increased lower extremity arterial stiffness but, also, with increased aortic stiffness. This suggests that one of the mechanisms of increased cardiovascular risk in people with lower extremity arteries incompressibility can be increased rigidity of the aorta, which, by increased aortic impedance, increases systolic blood pressure in the aorta resulting in increased left ventricular afterload and, subsequently, left ventricular hypertrophy. Interventions aimed at reducing aortic stiffness in patients with high ABI could possibly reduce their cardiovascular risk.

1. Úvod

Cévní systém má dvě základní funkce - vést krev od srdce do periférie (vodivá funkce – „conduit function“) a snižovat oscilace tlaku a průtoku způsobené cyklickou prací srdce (nárazníková funkce – „buffering function“) (Doobay, Anand, 2005). Nárazníková funkce snížením oscilací tlaku a průtoku zabezpečuje kontinuální perfuzi v periférii a zamezuje poškození mikrocirkulace pulzatilní energií (Mitchell, 2008). Zvyšování cévní tuhosti narušuje nárazníkovou funkci cévní stěny, což má patologické důsledky jak pro myokard, tak pro periferní cirkulaci.

Z funkčního hlediska lze tepenné řečiště rozdělit na centrální tepny elastického typu, periferní tepny muskulárního typu, které se postupně větví až na tepny drobného kalibru, a na rezistenční řečiště tvořené arteriolami. Centrální tepny, tj. aorta, krkavice a koronární tepny, mají v cévní stěně velké množství elastinu a kolagenu, přičemž celkový obsah vaziva převažuje nad hladkou svalovinou. Proto je nárazníková funkce typická pro velké tepny elastického typu. Stěna periferních tepen je tvořena hladkou svalovinou, elastinem a kolagenem. Tyto tepny zastávají hlavně vodivou funkci. Ve stěně arteriol je velké množství hladké svaloviny, což spolu s jejich malým průměrem má za následek, že malá změna svalového tonu způsobí velký vzestup periferní rezistence.

Rychlost šíření pulzové vlny na aortě (aortic pulse wave velocity, aPWV) jako parametr aortální tuhosti je nezávislým prediktorem kardiovaskulární morbidity a mortality pacientů s různým kardiovaskulárním rizikem (Laurent, Boutouyrie, 2007). Tuhost ostatních cév elastického a muskulárního typu má omezenou, nebo žádnou hodnotu v predikci kardiovaskulárního rizika. V řadě studií byla tuhost karotických tepen schopna predikovat kardiovaskulární riziko u osob s terminálním renálním onemocněním (Blacher et al., 1998) i po transplantaci ledvin (Barenbrock et al., 2002), ale neměla žádnou aditivní prediktivní hodnotu u osob s manifestním kardiovaskulárním onemocněním (Dijk et al., 2005). U osob s terminálním renálním onemocněním nebyly tuhost brachiální tepny a tepen dolních končetin schopny predikovat kardiovaskulární riziko (Pannier et al., 2005).

Z omezeného množství dat o tuhosti tepen dolních končetin se zdá, že jejich zvýšená tuhost není spojena s vyšším kardiovaskulárním rizikem. Na druhé straně je zvýšená tuhost tepen dolních končetin úzce spojena se symptomy ischemické choroby dolních končetin (Taniwaki

et al., 2001). Zvýšená tuhost tepen dolních končetin, měřená mezi brachiální tepnou a kotníkem, byla u diabetiků 2. typu spojena se sníženým průtokem v popliteální tepně (Suzuki et al., 2001). V jiné studii byla zvýšená tuhost popliteální tepny spojena s nižší hodnotou transkutánního kyslíku měřeného v oblasti nártu (Kizu et al., 2003). Z uvedeného vyplývá, že zvýšená tuhost tepen dolních končetin má vliv na průtok – tedy na vodivou funkci tepen. Přitom nelze vyloučit, že u daného pacienta zvýšená tuhost tepen, tedy arterioskleróza, nekoinciduje s aterosklerotickým postižením tepen.

Poměr kotník-paže je používán v diagnostice poruchy vodivé funkce tepen dolních končetin – v diagnostice ischemické choroby dolních končetin. Snížený kotníkový tlak ukazuje s vysokou senzitivitou a specificitou na ≥ 50% obstrukci lumina tepny (Fowkes, 1988, Lijmer et al., 1996). Vzhledem ke generalizovanému aterosklerotickému postižení u osob s ischemickou chorobou dolních končetin (Clement et al., 2000) je nízký ABI současně spojen se zvýšeným kardiovaskulárním rizikem (Heald et al., 2006, Wautrecht et al., 2006). V současné době se ukazuje, že i zvýšený kotníkový tlak nad 175 mm Hg je spojen s vyšším kardiovaskulárním rizikem, a to nezávisle na brachiálním krevním tlaku a jiných rizikových faktorech. V práci Hietanena a spol. byl zvýšený kotníkový tlak nezávislým prediktorem celkové a kardiovaskulární mortality u osob středního věku (Hietanen et al., 2008). V jiné práci kotníkový tlak přispíval ke zvýšení kardiovaskulárního rizika stanoveného pomocí klasických rizikových faktorů (měl aditivní prediktivní hodnotu) (Hietanen et al., 2011).

Zvýšená tuhost tepen dolních končetin diagnostikovaná pomocí rychlosti šíření pulzové vlny nebyla spojena se zvýšeným kardiovaskulárním rizikem (Pannier et al., 2005). Paradoxně je ale zvýšená tuhost tepen dolních končetin diagnostikovaná pomocí zvýšeného ABI (tedy zvýšeného kotníkového systolického tlaku) spojena se zvýšeným kardiovaskulárním rizikem, zvýšenou hmotností levé komory, a s vyšším rizikem chronického renálního onemocnění (Ix et al., Criqui et al., 2010, Liu et al., 2011). Falešně zvýšený ABI je projevem inkompresibility tepen dolních končetin a jejich zvýšené tuhosti na podkladě mediokalcinózy (Micheletti et al., 2008). Mediokalcinóza neboli Monckebergerova skleróza je způsobena depozicí kalcia v medii a vnitřní elastické membráně muskulárních tepen (Micheletti et al., 2008) jako důsledek dysregulace inhibice a stimulace kalcifikace (Johnson et al., 2006).

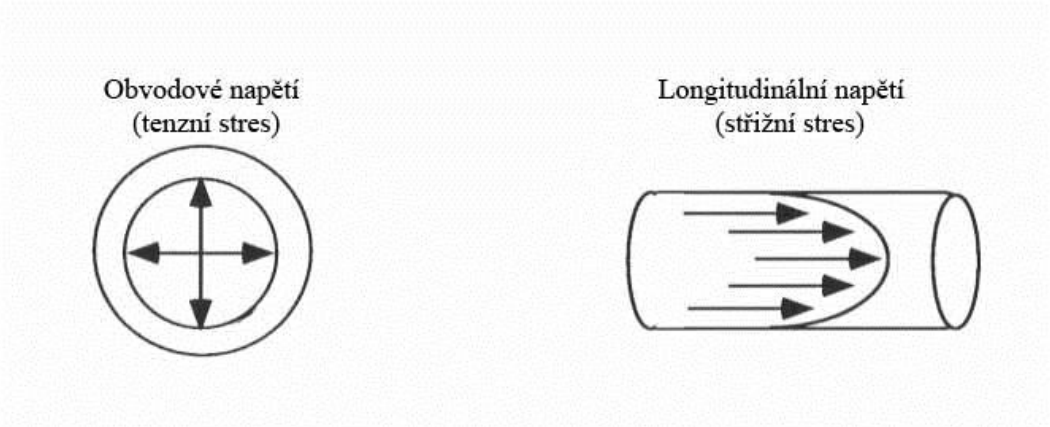
V současné době není známo, proč je zvýšení systolického kotníkového tlaku prediktorem kardiovaskulárního rizika, a proč samotná tuhost tepen dolních končetin nemá výpovědní hodnotu v predikci kardiovaskulárního rizika.

2. Přehled problematiky

2.1 Arteriální elasticita a tuhost

Teorie elasticity se zabývá vlivem aplikované síly a vzniklé deformace. Mechanické podněty pro remodelaci cévní stěny se označují jako napětí (*stres*). Napětí je definováno silou aplikovanou na jednotku plochy ($\sigma = F/A$). Podle směru aplikované síly rozeznáváme obvodové a longitudinální napětí (Nichols et al., 2005). Distribuce napětí v cévní stěně má významné důsledky na její funkci (Wang et al., 2009). Cévy reagují na změnu napětí adaptací, což stabilizuje průtok a obvodové napětí (Glagov, 1994). Obvodové napětí cévní stěny, označované také jako *tenzní stres*, je způsobeno tlakovou vlnou a působí kolmo na cévní stěnu. Podle Laplaceova zákona je přímo úměrné krevnímu tlaku a poloměru cévy a nepřímo úměrné tloušťce stěny. Zvýšení tenzního stresu vede k hypertrofii medie, což snižuje tenzní stres. Longitudinální napětí neboli *střižní stres* (shear stress) působí podél cévní stěny a je dáno třecí silou vyvolanou proudovou vlnou. Je přímo úměrné rychlosti proudění krve a její viskozitě a nepřímo úměrné poloměru cévy. Vysoký střižní stres je při normální funkci endotelu stimulem pro produkci vazodilatačních substancí, což zvyšuje průměr tepny a snižuje střižní stres (Li et al., 2005).

Obrázek 1. Směr sil způsobujících obvodové a longitudinální napětí. Tenzní napětí je způsobeno transmurálním tlakovým gradientem a působí kolmo na cévní stěnu. Longitudinální napětí je způsobeno třením a působí na endoteliální buňky v směru toku krve. Upraveno podle (Ballermann et al., 1998).



Deformace tělesa (ε), označována i jako „strain“, je změna tvaru vlivem působící síly. Je definována jako procentuální změna délky/poloměru vlivem aplikované síly. Pokud těleso nabyde po odstranění působící síly původní tvar, je elastické. Pokud si po odstranění působící síly předmět zachovává deformaci, je plastický. Cévní stěna má vlastnosti elastické i plastické v závislosti na působícím tlaku, proto mluvíme o viskoelastických vlastnostech cévní stěny (Cavalcante et al., 2011). Poměr napětí a deformace je parametrem elasticity; je označován jako elastický modulus (Yangův modulus) (London, Pannier, 2010). U většiny předmětů je tento vztah nelineární a sklon křivky zrcadlí vnitřní elastické vlastnosti cévní stěny.

Arteriální tuhost lze zjednodušeně označit jako odpor proti deformaci. V biomechanice rozlišujeme lokální a regionální parametry cévní tuhosti. Regionálními parametry jsou poddajnost (compliance) a roztažnost (distensibility). Poddajnost je definována jako změna objemu daného cévního objemu (ΔV) při změně tlaku (ΔP). Za předpokladu, že céva má konstantní délku, lze objem nahradit průměrem (A), tedy C= ΔA/ΔP. Roztažnost (D) je relativní změna plochy způsobená změnou tlaku [D= ΔA/(ΔP x A_0)]. Vztah tlaku a objemu není lineární. Za nízkého tlaku se uplatňují především elastická elastinová vlákna, zatímco za vysokého tlaku tužší kolagenová. Z toho vyplývá, že poddajnost a roztažnost mohou být definovány pouze v souvislosti s konkrétní hodnotou tlaku (Caputo et al., 1992). Regionálním parametrem tuhosti je rychlost šíření pulzové vlny (pulse wave velocity, PWV).

2.2 Buněčné a molekulární determinanty arteriální tuhosti

Medie arteriální stěny je tvořena hladkými svalovými buňkami a extracelulární matrix. Strukturální integrita a elasticita stěny velkých tepen elastického typu závisí na vzájemném poměru a prostorovém uspořádání dvou hlavních proteinů – kolagenu a elastinu (Laurent et al., 2005). Elastin je odpovědný za pružnost cévní stěny, přičemž kolagen zaručuje pevnost (kolagen má 5 000x vyšší elastický modulus než elastin (Lee, Kamm, 1994)). Za normálních podmínek nejsou kolagenová vlákna elastických tepen pod napětím, a proto neovlivňují rigiditu cévy. K jejich distenzi dochází až při výrazné

dilataci cévy. Kvalitativní a kvantitativní změny elastických vláken proto mají vliv na rigiditu cévní stěny.

Základem morfologických změn při stárnutí i při hypertenzi je mechanické opotřebování elastických artérií. To se projevuje desorganizací pravidelné struktury elastických vláken a lamel, jejich ztenčením, štěpením a fragmentací (Lakatta, 1993). Hypertenze vede k urychlení procesu stárnutí tepen zvýšenou tlakovou zátěží (Safar, 1994). Změny způsobené mechanickým opotřebováním cév (arterioskleróza) je třeba odlišit od aterosklerózy. Rozdíly mezi těmito dvěma procesy jsou následující: ateroskleróza je nerovnoměrný proces lokalizovaný na určitý úsek cévy, zatímco mechanické opotřebování vede k difuzním změnám, k nimž dochází především v centrálních tepnách elastického typu. Ateroskleróza vzniká a rozvíjí se hlavně v intimně, arterioskleróza je primárně procesem cévní medie. Ateroskleróza vede ve většině případů k zúžení cévy a distální ischémii, zatímco arterioskleróza vede k dilataci cév a snížení jejich poddajnosti. Ve věku nad 80 let je plocha aorty 3-4x větší než u 20letého jedince (Mitchell, Adams, 1977).

Degenerace elastických vláken vlivem mechanického stresu vede ke zvýšení podílu kolagenu v cévní stěně i k depozici kalcia. Často dochází i k infiltraci hladkých svalových buněk, makrofágů a mononukleárů, které produkují matrix metaloproteinázy (MMP) a cytokinin (Zieman et al., 2005). Chronický zánět zvyšuje cévní tuhost prostřednictvím endoteliální dysfunkce (snížením dostupnosti NO), uvolněním metaloproteináz (například MMP-9), kalcifikací cévní medie, změnou zastoupení proteoglykanů, a infiltrací okolí vasa vasorum s následnou ischémii cévní stěny (McEniery, Wilkinson, 2005).

Relativní zastoupení kolagenu a elastinu v cévní stěně je řízeno dynamickým procesem produkce a degradace. Deregulace této rovnováhy, například v důsledku zánětu, vede k nadprodukci abnormálního kolagenu a ke snížení relativního zastoupení normálního elastinu, což zvyšuje aortální tuhost (Johnson et al., 2001). Degradace kolagenu a elastinu probíhá prostřednictvím katabolických MMP. Buňky cévní stěny, makrofágy a polymorfonukláry produkují kolagenázy (MMP-1, MM-8, MMP-13), elastázy (MMP-7) a gelatinázy (MMP2, MMP-9) (Jacob, 2003).

Jedním z mechanismů zvýšení cévní rigidity u diabetiků a pacientů s poruchou glukózové tolerance je cross-linking (zkřížená vazba) neenzymatickou glykací. Kolagenová vlákna spojená pokročilými konečnými produkty glykace **(**advanced

glycation end products; AGE) jsou tužší a odolnější k hydrolýze, což vede k akumulaci strukturálně abnormálních molekul kolagenu (Verzijl et al., 2000). AGE vedou k endoteliální dysfunkci, zvyšují produkci kyslíkových radikálů, prozánětlivých cytokinů, růstových faktorů a adhezních molekul. U diabetiků a pacientů s chronickým renálním onemocněním dochází k aktivaci systémového a lokálního systému renin-angiotenzin. To vede k hypertrofii buněk hladké svaloviny, aktivaci zánětu a vzestupu produkce kolagenu. U jedinců s onemocněním ledvin zvyšují kalcifikace v medii tepen významně cévní tuhost.

Na rozdíl od aorty mají věk, obezita, hypertenze a diabetes pouze malý vliv na průměr brachiální a radiální tepny (Benjamin et al., 2004), ale vedou k nárůstu jejich tloušťky (Hayoz et al., 1992). Hypertenze paradoxně snižuje nebo nemění tuhost brachiální a radiální tepny (Laurent et al., 1994, Laurent, 1995, Mourad et al., 1998). To lze vysvětlit hypertrofií relativně pružných hladkých svalových buněk, na které je přenášen tah místo tužších komponent cévní stěny jako je kolagen (Laurent, 1995, Laurent et al., 2005). Podobně i věk a diabetes snižují nebo nemění tuhost brachiální tepny (van der Heijden-Spek et al., 2000, Cameron et al., 2003). Hypertrofie a remodelace periferních svalových tepen může kompenzovat celkově sníženou poddajnost tepenného systému způsobenou nárůstem aortální tuhosti (Mitchell et al., 2001).

2.3 Vliv tuhosti aorty na myokard

Funkcí srdce je čerpat krev a zajistit tak dostatečný přísun živin. Činnost srdce je cyklická, ale požadavky tkání na dodávku živin jsou kontinuální. Nárazníková funkce velkých cév umožňuje přeměnu pulzatilního toku krve způsobenou cyklickou srdeční akcí na kontinuální tok (Nemes et al., 2008). Z fyzikálního hlediska dochází k přeměně kinetické energie v energii potenciální (polohovou). Aorta tedy slouží jako rezervoár krve pro diastolu. Až polovina z tepového objemu během systoly zůstává v aortě (Bader, 1983). Po uzavření aortální chlopně v diastole klesá tlak v aortě, což vede k elastické retrakci aorty a vypuzení krve do periférie. To zabezpečuje kontinuitu toku v diastole. Elastická aorta proto snižuje centrální systolický tlak a zvyšuje diastolický tlak (O'Rourke, 1990). Zvýšení tuhosti aorty je spojeno s dilatací aorty a zvýšením její objemové kapacity aorty, což snižuje schopnost aorty vypuzovat krev do periférie.

V elastické aortě se vlna odražená z periférie vrací do ascendentní aorty v časné diastole, což zvyšuje diastolický tlak. Výška diastolického tlaku ovlivňuje koronární perfuzi, která probíhá ve fázi srdeční diastoly (O'Rourke, 1990). Zvýšení tuhosti aorty významně zvyšuje centrální systolický a pulzní tlak prostřednictvím zvýšení charakteristické impedance a rychlosti návratu odražené vlny (Borlaug et al., 2007, McEniery et al., 2008). Charakteristická impedance ascendentní aorty ovlivňuje výši vzestupu tlaku v aortě způsobeného vypuzením krve z levé komory. V intervalu asi 100 ms v aortě mladého člověka s charakteristickou impedancí 500 dyn.s.cm^{-3} stoupne krevní tlak o 20 mm Hg, kdežto u staršího jedince s charakteristickou impedancí aorty 1000 dyn.s.cm^{-3} stoupne tlak v aortě o 40 mm Hg (Wilkinson et al., 2001). Časný návrat odražené vlny z periférie vede k pozdnímu systolickému zvýšení tlaku asi o 30 mm Hg. To znamená, že během systoly se tlak v tuhé aortě zvyšuje o 70 mm Hg, kdežto v elastické aortě pouze o 20 mm Hg. Méně než dvojnásobné zvýšení brachiálního pulzního tlaku s věkem podhodnocuje troj- až čtyřnásobné zvýšení aortálního pulzního tlaku (Franklin et al., 1997). To vysvětluje, proč je centrální tlak v těsnějším vztahu s echokardiografickými a EKG parametry hypertrofie LK než tlak brachiální (Roman et al., 2010, Wohlfahrt et al., 2011). Zvýšení centrálního systolického a pulzního tlaku s nárůstem aortální tuhosti vedou ke zvýšení afterloadu (dotížení) levé komory (Pasipoularides, 2007). To způsobuje hypertrofii levé komory a zvyšuje požadavky srdce na dodávku kyslíku. Snížení diastolického tlaku snižuje koronární perfuzi, jejímž důsledkem může být subendokardiální ischémie. Hypertrofie levé komory spolu se sníženým transmyokardiálním tlakovým gradientem způsobeným nízkým diastolickým tlakem snižují koronární rezervu. U osob se středně významnou stenózou koronárních tepen je tuhost aorty jednou z hlavních determinant ischemického prahu (Eberhardt et al., 1990).

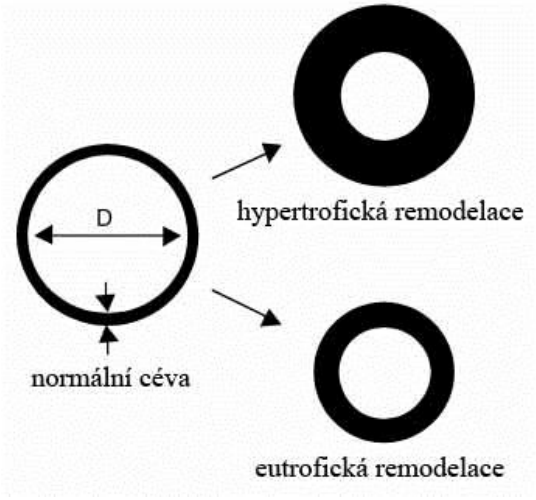
2.4 Vliv aortální tuhosti na mikrocirkulaci

Funkcí mikrocirkulace, tedy cév menších než 300 μm, je regulovat krevní tok s cílem pokrýt metabolické potřeby tkání a snížit tlakovou zátěž na fragilní kapiláry (Mourad et al., 1998, O'Rourke, Safar, 2005). Vysoká rezistence mikrocirkulace zajišťuje výrazný pokles středního arteriálního tlaku a kontinuální tok krve v mikrocirkulaci (Koller, 2002, O'Rourke, Safar, 2005). Dysfunkční mikrocirkulace způsobuje zvýšení kapilárního tlaku s následnou hyperfiltrací, únikem proteinů, otoky, a

poškozením kapilár (Mitchell, 2008). Celková rezistence mikrocirkulace spolu se srdečním výdejem ovlivňují střední arteriální tlak. Z krátkodobého hlediska je napětí hladkých svalů v oblasti mikrocirkulace důležité pro regulaci průtoku krve, což má obzvláštní význam v orgánech s autoregulací, jako je mozek nebo ledviny. Vzestup pulzního tlaku vede ke kontrakci svalových buněk a ke zvýšení rezistence vůči proudění, což stabilizuje perfuzi. Na druhou stranu ale dlouhodobé zvýšení tonu mikrocirkulace vede k remodelaci cév, což snižuje napětí cévní stěny a posouvá tonus na novou nominální hodnotu za cenu zvýšení celkové rezistence mikrocirkulace (Jacobsen et al., 2008, Kalaria, 2009). Malé proximální cévy s relativně nízkým svalovým tonem hypertrofují a zmenšují svůj vnitřní lumen (hypertrofická remodelace). Malé distální cévy s vyšší myogenní odpovědí zmenšují svůj lumen, ale nemění tloušťku cévní stěny (eutrofická remodelace). Jak hypertrofická, tak eutrofická remodelace zvyšují poměr mezi tloušťkou cévní medie a průměrem tepny (poměr medie/lumen). To snižuje průtokovou rezervu, protože i při maximální vazodilataci má remodelovaná céva menší lumen. Zvýšený poměr medie/lumen je nezávislým prediktorem kardiovaskulárního rizika (Rizzoni et al., 2003).

Obrázek 2. Eutrofická a hypertrofická remodelace cévní stěny

U hypertrofické remodelace dochází k zvýšení tloušťky cévní medie a tím ke zmenšení vnitřního lumenu cévy. U eutrofické remodelace se nemění plocha průřezu cévní stěny, ale zmenšuje se vnitřní průměr tepny. Upraveno podle (New et al., 2004).



Studie u zvířat i u lidí ukázaly, že svalové napětí (Mellander, Arvidsson, 1974, Loutzenhiser et al., 2002), remodelace (Christensen, 1991, Baumbach, 1996) a endoteliální funkce (Ceravolo et al., 2003) mikrocirkulace závisí na pulzním tlaku více než na středním arteriálním tlaku. Zvýšení svalového napětí a remodelace chrání mikrocirkulaci před barotraumatem způsobeným zvýšeným systolickým a pulzním tlakem (Loutzenhiser et al., 2006), které jsou důsledkem zvýšené aortální tuhostí. Hypotéza vztahu struktury a funkce mikrocirkulace s aortální tuhostí byla potvrzena ve velkých populačních studiích (Liao et al., 2004, Mitchell et al., 2005, Cheung et al., 2007). Rozdílná tuhost aorty a periferních muskulárních tepen způsobuje vznik odražené vlny, což chrání mikrocirkulaci před pulzatilním tokem. Nárůst aortální tuhosti vede k pulzatilnímu barotraumatu v orgánech s vysokým průtokem, jako jsou mozek a ledviny (Vyas et al., 2007). To potvrzují i nedávno publikované studie, ve kterých byly zvýšený pulzní tlak (PP) a aortální tuhost spojeny s poklesem kognitivních funkcí (Hanon et al., 2005, Scuteri et al., 2007).

2.5 Vyšetření aortální tuhosti

2.5.1 Regionální parametr cévní tuhosti

Rychlost šíření pulzové vlny (PWV) je regionálním parametrem cévní tuhosti. Pro svou jednoduchost, neinvazivnost, přesnost a reprodukovatelnost je považována za zlatý standard vyšetření cévní tuhosti (Lehmann et al., 1993, Asmar et al., 1995, Asmar et al., 1997, Laurent et al., 2006). PWV charakterizuje míru rigidity příslušného úseku tepenného řečiště: čím rychleji se tlaková vlna šíří, tím tužší je vyšetřovaná céva. Rychlost šíření pulzové vlny se vypočítává jako podíl doby šíření pulzové vlny mezi dvěma místy a vzdálenosti mezi těmito dvěma místy. K výpočtu rychlosti pulzové vlny lze využít tlakovou (Asmar et al., 1995) a distenzní vlnu (van der Heijden-Spek et al., 2000) nebo dopplerovský záznam (Chiu et al., 1991). Vzhledem k tomu, že na nárazníkové funkci cév se nejvíce podílejí hrudní a břišní aorta (Latham et al., 1985, Isnard et al., 1989), a v populačních studiích byla tuhost aorty lepším prediktorem kardiovaskulárního rizika než tuhost jiných tepen (Blacher et al., 1999, Laurent et al., 2001, Cruickshank et al., 2002), má vyšetření rychlosti pulzové vlny na aortě největší význam (Laurent et al., 2006). Rigidita je dána především stavem cévní medie, tj. preaterosklerotickými změnami a stupněm hypertrofie cévní stěny. Tvorba

sklerotických plátů ovlivňuje PWV již málo. Při měření je třeba vzít v úvahu krevní tlak: vysoký krevní tlak zvyšuje rigiditu tepny.

2.5.2 Lokální parametry cévní tuhosti

K vyšetření lokální cévní tuhosti se používají povrchově uložené tepny, nejčastěji karotické tepny, a vyšetření se provádí pomocí ultrazvuku (Hoeks et al., 1990, Tardy et al., 1991). Tuhost hluboko uložených tepen lze vyšetřit pomocí magnetické rezonance (Bolster et al., 1998). Poddajnost (C) tepen se vypočítává z tlakového rozdílu mezi systolou a diastolou a ze změny průměru tepny v systole a diastole. Rychlost šíření pulzové vlny lze vypočíst z poddajnosti pomocí Brawellova-Hillova vzorce. Poddajnost je přímo úměrná druhé mocnině PWV. Nevýhodou vyšetření lokální cévní tuhosti je nutnost technicky vyspělých přístrojů a časová náročnost. Proto se tato metoda používá hlavně k mechanistickým analýzám v patofyziologii a farmakologii. K určení změny průměru tepny lze využít radiofrekvenční analýzu ultrazvukového signálu, která má rozlišovací schopnost 1 μm (Hoeks et al., 1990). Standardní vyšetření ultrazvukem je limitováno velikostí pixelu, která je 150 μm (Girerd et al., 1998). Vyšetřením pomocí „echotrackingu“ lze určit tlakovo-průměrovou křivku tepny, tedy určit tuhost tepny při daném tlaku (Hayoz et al., 1992, Laurent et al., 1993, Laurent et al., 1994, Bussy et al., 2000), a z časového rozdílu tlakových křivek sousedících bodů lze určit lokální PWV (Meinders et al., 2001). Výhodou této metody je také možnost určit vztah mezi geometrickými změnami cévy a arteriální tuhostí. Vzhledem k možné chybě vlivem amplifikace pulzního a systolického tlaku v cévách je při stanovení cévní tuhosti nutno použít lokální, a nikoliv brachiální krevní tlak. Lokální tlak lze odvodit pomocí aplanační tonometrie vyšetřované cévy kalibrací na brachiální krevní tlak integrací radiální pulzové vlny (Kelly, Fitchett, 1992, Verbeke et al., 2005) nebo pomocí převodní funkce (transfer function) integrované v přístroji SphygmoCor (AtCor Medical Ltd., West Ryde, New South Wales, Australia).

2.6 Kotníkový krevní tlak a poměr kotník-paže

Za normálních okolností je kotníkový krevní tlak měřený na *a. dorsalis pedis* nebo na *a. tibialis posterior* vleže o 10 % vyšší než krevní tlak měřený na paži. Tento rozdíl je vysvětlován amplifikací pulzního tlaku s narůstající vzdáleností od srdce

(Nichols WW, 1991). Za normální hodnotu poměru tlaků v oblasti kotníku a na paži (ankle/brachial index, ABI) se považuje ABI v rozmezí 1–1,3. Vyšetření ABI se již 100 let používá k diagnostice vodivé poruchy cév dolních končetin. V práci Lijmera (Lijmer et al., 1996) měl ABI < 0,91 senzitivitu 79 % a specificitu 96 % v detekci více než 50% stenózy tepen dolních končetin při angiografii. Podobně Fowkes (Fowkes, 1988) nalezl 95% senzitivitu a 100% specificitu ABI < 0,9 v diagnostice významné stenózy tepen dolních končetin.

Aterosklerotické postižení tepen dolních končetin je obvykle spojeno s aterosklerózou i v ostatních částech tepenného řečiště (Clement et al., 2000). Nízký ABI je proto známkou vysokého kardiovaskulárního rizika. Přibližně 60–80 % nemocných s ischemickou chorobou dolních končetin má při koronarografii významnou stenózu minimálně jedné koronární tepny (Dormandy et al., 1989, Valentine et al., 1994, Mendelson et al., 1998). Metaanalýza klinických studií (Heald et al., 2006), do které bylo zařazeno více než 45 000 pacientů z 11 populačních studií, ukázala vyšší riziko celkové mortality (RR 1,6; 95% CI 1,32–1,95), kardiovaskulární mortality (RR 1,96; 95% CI 1,46–2,64), infarktu myokardu (RR 1,45; 95% CI 1,08–1,93) a cévní mozkové příhody (RR 1,35; 95% CI 1,10–1,65) u pacientů s ABI < 0,9 po adjustaci na věk, pohlaví, kardiovaskulární rizikové faktory a kardiovaskulární onemocnění, ve srovnání s pacienty s normálním ABI. Z toho vyplývá, že ABI dokáže zpřesnit stratifikaci kardiovaskulárního rizika založenou na tradičních rizikových faktorech.

Zvýšený ABI (nad 1,3) ukazuje na zvýšenou tuhost tepen dolních končetin, která je způsobena nestlačitelností tepen při vyšetření kotníkových tlaků. Inkompresibilita tepen dolních končetin je nejčastěji způsobena kalcifikací medie – mediokalcinózou, která je častá u lidí s chronickým ledvinovým onemocněním a diabetem.

2.7 Centrální a brachiální krevní tlak

V elastických a velkých muskulárních tepnách je střední arteriální krevní tlak (MAP) téměř konstantní, což je způsobeno nízkým odporem toku velkých cév a jejich relativně velkým průměrem. Hodnota MAP je ovlivněna srdečním výdejem (CO) a periferní rezistencí (PR) podle rovnice MAP = CO × PR. Periferní rezistence je ovlivněna vasomotorickým tonem periferních cév malého kalibru. Vlivem cyklické srdeční akce osciluje krevní tlak kolem MAP, přičemž maximem a minimem oscilací je

systolický, resp. diastolický krevní tlak. Velikost výchylky od MAP je ovlivněna vstupní impedancí. Vstupní impedance vyjadřuje míru odporu cirkulace proti oscilačnímu proudění krve a integruje parametry působící proti vypuzování krve z levé komory. Vstupní impedance je ovlivněna periferní cévní rezistencí, viskolelastickými vlastnostmi a rozměry aorty i velkých cév, a intenzitou a načasováním odražené tlakové vlny (London, Pannier, 2010). Periferní systolický a pulzní tlak je vyšší než centrální tlak. Tento fenomén se nazývá amplifikace systolického a pulzního tlaku. Pro amplifikaci tlaku existují dva důvody (Schillaci, Grassi, 2010). Prvním je progresivní nárůst tuhosti tepen směrem od srdce do periférie, proto je amplituda dopředné pulzové vlny vyšší v periférii než v aortě. Druhým důvodem je časnější střet s odraženou vlnou vznikající v periférii – v místech větvení a s rozdílnou tepennou tuhostí. Výši centrálního tlaku není možno předvídat na základě periferního tlaku (Camacho et al., 2004). Je to způsobeno množstvím faktorů ovlivňujících amplifikaci tlaku. Amplifikace tlaku je ovlivněna věkem (Wilkinson et al., 2001), polohou těla, srdeční frekvencí, a krevním tlakem (Wilkinson et al., 2000, Wilkinson et al., 2001). Rozdíl mezi centrálním a brachiálním krevním tlakem se s věkem snižuje přibližně do 50 až 60 let, následně zůstává rozdíl přibližně konstantní. Průměrný rozdíl mezi brachiálním a aortálním tlakem u mužů je 11 mmHg, a 8 mmHg u žen (McEniery et al., 2008). To vysvětluje, proč má izolovaná systolická hypertenze v adolescenci a stáří úplně stejný periferní a rozdílný centrální hemodynamický profil (Hulsen et al., 2006, Wallace et al., 2007). Centrální (aortální) krevní tlak představuje skutečnou tlakovou zátěž levé komory. To potvrzuje i nedávno publikovaná studie, ve které byla hmotnost levé komory stanovená pomocí echokardiografie v těsnějším vztahu s centrálním než brachiálním tlakem (Roman et al., 2010). V longitudinálních studiích byl centrální tlak lepším prediktorem kardiovaskulárního rizika než brachiální tlak (Safar et al., 2002, Chirinos et al., 2005, Pini et al., 2008, Wang et al., 2009).

3. Hypotéza

Vzhledem k rozdílné histologické struktuře tepen dolních končetin a aorty předpokládáme, že se faktory ovlivňující cévní tuhost v obou oblastech budou lišit. Lze předpokládat, že zvýšení tuhosti tepen dolních končetin projevující se jejich inkompresibilitou při vyšetření poměru kotník-paže bude souviset se zvýšením tuhosti aorty. Je známo, že vyšší aortální tuhost zvyšuje vstupní aortální impedanci, což vede k hypertrofii levé komory. Domníváme se tedy, že zvýšený kotníkový systolický tlak souvisí s vyšší aortální tuhostí, což by vysvětlovalo jeho prediktivní hodnotu nezávislou na brachiálním tlaku. Lze předpokládat, že centrální tlak v ascendentní aortě, determinovaný mimo jiné aortální tuhostí, bude mít větší vliv na hypertrofii levé komory srdeční než brachiální krevní tlak.

4. Cíl práce

1. Porovnat oscilometrickou a dopplerovskou metodu stanovení poměru kotník-paže

2. Zjistit faktory ovlivňující tuhost tepen dolních končetin a porovnat je s faktory ovlivňujícími tuhost aorty (zarovnat)

3. Zjistit vliv přidání tuhosti tepen dolních končetin k tuhosti aorty na asociaci s kardiovaskulárními rizikovými faktory a manifestním kardiovaskulárním onemocněním

4. Navrhnout možné mechanizmy spojující zvýšený poměr kotník-paže s hypertrofií levé komory

5. Zjistit vztah mezi hypertrofií levé komory diagnostikované pomocí elektrokardiografických kritérií a centrálním i brachiálním krevním tlakem

5. Metodika

Použité metody a soubory pacientů jsou podrobně popsány v přiložených publikacích.

Populace

Pro analýzy jsme použili náhodně vybraný 1% vzorek české populace ve věku 25-75 let vyšetřený v rámci studie Czech post-MONICA z okresu Plzeň město.

Poměr kotník-paže

Měření poměru kotník-paže jsme prováděli pomocí přístroje BOSO ABI (BOSO ABI 100, Bosch+Sohn, Jungingen, Německo) a ručního dopplerovského přístroje (Dopplex multi, Huntleigh, Cardiff, UK).

Rychlost šíření pulzové vlny

Pomocí přístroje SphygmoCor (AtCor Medical Ltd, West Ryde, New South Wales, Australia) jsme měřili karoticko-femorální (aPWV) a femoro-tibiální (lePWV) rychlost šíření pulzové vlny. Princip vyšetření spočívá ve stanovení časového posunu (Δt) začátku tlakové vlny mezi dvěma místy, které jsou od sebe ve vzdálenosti D. Rychlost šíření pulzové vlny se vypočítavá jako poměr vzdálenosti (D) a času (Δt). Výsledná hodnota je uváděna v metrech za sekundu. Jednotlivé pulzové vlny jsou snímány transkutánně pomocí sondy aplanačního tonometru po dobu 20 vteřin. Měření se provádí za současného monitorování EKG. Při tomto sekvenčním měření se časový posun jednotlivých pulzových vln určuje ve vztahu k R-kmitu na EKG záznamu. Parametr arteriální tuhosti BETA jsme odvodili z PWV pomocí vzorce BETA = ln (systolický / diastolický tlak) × 2 viskozita krve / tlaková amplituda × PWV2.

Ke statistické analýze dat jsme použili statistický program SPSS verze 16 (Chicago, IL, USA). Použité statické metody jsou podrobně popsány v jednotlivých publikacích.

6. Vlastní výsledky výzkumné práce

6.1 Srovnání oscilometrické a dopplerovské metody stanovení poměru kotník-paže

Stanovení poměru kotník-paže (ABI) pomocí dopplerovské metody se používá v diagnostice ischemické choroby dolních končetin (ICHDK). Výhodou dopplerovského vyšetření je vysoká senzitivita a specificita v diagnostice ICHDK (Ouriel et al., 1982, Fowkes, 1988, Lijmer et al., 1996). V běžné klinické praxi se toto vyšetření využívá pouze sporadicky, ačkoliv je součástí doporučení odborných společností (Mancia et al., 2013). Použití automatických přístrojů pro měření ABI by mohlo zjednodušit vyšetření a zlepšit dostupnost tyto metody. Cílem práce bylo porovnat nový automatický oscilometrický přístroj pro měření ABI s tradiční dopplerovskou metodou.

Metodika Do studie bylo zařazeno 839 pacientů ze studie Czech post-MONICA (náhodně vybraný reprezentativní vzorek české populace ve věku nad 25 let) průměrného věku 54,3 ± 13,8 let, 47 % souboru tvořili muži. Měření poměru kotník-paže jsme prováděli pomocí přístroje BOSO ABI (BOSO ABI 100, Bosch+Sohn, Jungingen, Německo) a ručního dopplerovského přístroje (Dopplex multi, Huntleigh, Cardiff, UK) v náhodném pořadí. Výsledky jsme analyzovali pomocí testů dle Blanda a Altmana (Bland, Altman, 1986).

Výsledky Průměrný rozdíl v ABI mezi metodami byl 0,1 ± 0,1 (95% CI -0,11-0,30). Rozdíl mezi dopplerovskou a oscilometrickou metodou měření ABI se zvyšoval s rostoucí hodnotou ABI ($r = 0,29$, $p < 0,001$). Pokud jsme použili dopplerovské vyšetření jako zlatý standard diagnostiky ICHDK, mělo automatické oscilometrické měření ABI 77% senzitivitu, 98% specificitu, 37% pozitivní a 99,6% negativní prediktivní hodnotu při diagnostice ABI <0,9 v obecné populaci.

Diskuse Z výsledků naší práce provedené v náhodně vybraném vzorku české populace vyplývá, že hodnotu ABI stanovenou pomocí automatického oscilometrického zařízení BOSO ABI nelze zaměňovat se standardním dopplerovým měřením poměru kotník-paže. Rozdíl mezi dopplerovskou a oscilometrickou metodou měření ABI se zvyšuje s rostoucí hodnotou ABI, proto oscilometrická metoda není vhodná pro diagnostiku pacientů s inkompresibilitou tepen dolních končetin. Nicméně vysoká negativní prediktivní hodnota umožňuje použití oscilometrického přístroje BOSO ABI jako screeningového nástroje pro ICHDK, kde jedním z hlavních cílů je vyloučit

onemocnění. Minimální dovednosti a malá časová náročnost předurčuji oscilometrickou metodu měření ABI pro screening v klinické praxi.

Pozorovaný rozdíl mezi dopplerovskou a oscilometrickou metodou měření ABI lze částečně vysvětlit rozdílnou metodikou při oscilometrickém měření tlaku. Oscilometrická metoda přímo neměří systolický a diastolický tlak, ale vypočítává je pomocí výrobcem dosazené rovnice z naměřeného středního arteriálního tlaku. Střední arteriální tlak se přitom měří na základě oscilací tepny, které jsou závislé na různých faktorech, přičemž tuhost měřené tepny hraje jednu z nejdůležitějších rolí (van Popele et al., 2000). Vliv tuhosti kotníkových tepen na kotníkový tlak měřený oscilometricky může vysvětlit pozorované rozdíly v kotníkových tlacích mezi metodami. Většina studií porovnávajících oscilometrickou a dopplerovskou metodu měření ABI popsala podobné rozdíly mezi metodami (Ramanathan et al., 2003, Nukumizu et al., 2007, Aboyans et al., 2008). Jiné ukázaly dobrou shodu mezi metodami (Cortez-Cooper et al., 2003, Beckman et al., 2006). Naproti tomu většina studií, podobně jako my, ukázala vysokou negativní prediktivní hodnotu oscilometrické metody při stanovení nízkého ABI (Beckman et al., 2006, MacDougall et al., 2008, Mehlsen et al., 2008), což umožňuje využít tuto metodu pro screening ICHDK v klinické praxi. Vzhledem k systematickému podhodnocování vysokého ABI oscilometrickou metodou je pro diagnostiku inkompresibility tepen dolních končetin vhodnější dopplerovská metoda měření ABI.

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A novel oscillometric device for peripheral arterial disease screening in everyday practice. The Czech-post MONICA study

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Aim. **Ankle brachial index (ABI) is a diagnostic tool for peripheral arterial disease (PAD) and a cardiovascular risk stratification tool. Despite this evidence and guidelines recommending its use in everyday practice, ABI is not widely used. Automatic ABI measurement may lower the barrier to incorporate ABI measurement into everyday practice. The aim of this study was to validate a novel automatic oscillometric ABI device (BOSO ABI) against a gold standard-Doppler device in an epidemiological setting.**
Methods. **In 839 patients from the Czech post-MONICA study (a randomly selected representative population sample aged over 25 years), mean age 54.3±13.8 years (47% of men), ABI measurement was performed using the BOSO ABI device and a handheld Doppler device in a random fashion. The two techniques were carried out by different investigators each blinded to the findings of the other. Analyses were conducted as proposed by Bland and Altman.**
Results. **The mean ABI difference between the two methods was 0.1±0.11, with 95% limits of agreement ranging from -0.11 to 0.30. The difference between Doppler and oscillometric ABI increased significantly with increasing mean ABI (r=0.29; P<0.001). When considering Doppler the gold standard, automated oscillometric measurement had a 76.9% sensitivity, 97.9% specificity, and 37% positive and 99.6% negative predictive values in diagnosing ABI <0.9.**
Conclusion. **The BOSO ABI device cannot be used interchangeably for standard Doppler ABI measurement in diagnosing PAD. However, its high negative predictive value allows using it as a screening tool for PAD.**
[Int Angiol 2011;30:256-61]

Key words: **Peripheral arterial disease - Ankle-brachial index - Oscillometry - Ultrasonography, Doppler.**

ABI measurement has long been used by angiologists to diagnose peripheral arterial disease (PAD). ABI <0.9 has a 79-95% sensitivity and 96-100% specificity in establishing PAD in the lower extremities.[1-3] Recently, there has been growing evidence that PAD (even subclinical) is a strong predictor of future cardiovascular events. In a meta-analysis of 11 studies, ABI <0.9 was associated with increased risk of total and cardiovascular mortality, coronary heart disease, and stroke after adjustment for traditional risk factors.[4] In another meta-analysis, ABI improved the accuracy of cardiovascular risk prediction beyond the Framingham risk score.[5] In the latest European Society of Cardiology-European Society of Hypertension guidelines, ABI measurement is suggested for cardiovascular risk stratification.[6]

Despite this evidence and guidelines, ABI is not commonly used in general practice. The most common method used by general practitioners to diagnose PAD is a history of claudication and lower limb pulse palpation. Facts advocating against this practice are that the asymptomatic form of PAD is five times more common than the symptomatic one and also the poor sensitivity of pulse palpation to detect PAD. Likewise, the presence of pulse cannot definitely exclude PAD.[7-10]

ABI has traditionally been measured using a

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sphygmomanometer and a handheld continuous wave Doppler device. Time consumption and required skill are the most common reasons why ABI is underused in general practice. The accuracy of ABI measurement in everyday practice is another issue. ABI measurement skills significantly influence the reliability of Doppler measurement.[2, 11-13] The reproducibility of ABI measurement was much better when performed by an experienced observer than by a less experienced one. In everyday clinical practice, the validity is decreased due to multiple sources of error associated with the ABI measurement.[14, 15] An automated oscillometric device may overcome these problems and help introduce ABI examination into everyday practice of general practitioners.

To date, there has been only one study using the automated oscillometric technique on a large scale in an epidemiological setting.[16] There has been no study comparing the new automated oscillometric device (BOSO ABI-system 100, Bosch+Sohn GmbH & Co. KG, Jungingen, Germany) against standard Doppler technique. The advantage of this system, compared to others, is its ability to measure blood pressure on all extremities at a time, thus eliminating ABI measurement inaccuracy due to blood pressure fluctuation. In this paper, we evaluated the new automated oscillometric device against standard Doppler technique in a representative random population sample of the Czech post-MONICA study.

Materials and methods

Study population

The Czech post-MONICA study is a population survey studying trends and determinants of cardiovascular risk factors in a 1% random population sample of the Czech population in nine districts. The selection was made from the General Health Insurance company register keeping, by law, a list of all those insured. Health insurance is mandatory for all Czech citizens. Methods of the Czech post-MONICA study are described in detail elsewhere.[17] Our study includes 839 individuals aged over 25 years of the district of Plzeň (Pilsen), which represents 90.2% of all those examined in that district. The response rate was 68%.

Doppler ABI measurement

Appropriately sized cuffs of a mercury sphygmomanometer (Baumanometer, W.A.Baum Co. Inc., New York, NY, USA) were placed proximal to the malleolus and on the right arm. After a five-minute resting period in the supine position, systolic blood pressure was measured in the right brachial artery, right dorsal pedal and posterior tibial arteries, left dorsal pedal and tibial arteries (in this order) with a pocket Doppler device with an 8 MHz probe (Dopplex multi, Huntleigh, Cardiff, UK). Next, systolic blood pressure measurement was repeated on the right brachial artery for a second time. If the difference between the first and the second brachial systolic pressure measurements was higher than 10 mmHg, all measurements were repeated. All measurements were performed by two experienced physicians. The first audible signal was used to identify the systolic blood pressure at each location. The ABI was calculated for each leg by dividing the highest systolic ankle pressures by the first measured brachial systolic blood pressure.

Automated oscillometric ABI measurement

An automated oscillometric device (BOSO ABI-system 100) was used. This system includes four cuffs (2 leg and 2 arm cuffs each), allowing concomitant blood pressure measurement on all limbs. This prevents ABI measurement inaccuracy due to blood pressure fluctuation. Automated ABI readings for each leg were obtained in a quiet room, after 5 minutes of rest in the recumbent position. In 450 patients, another reading was performed 2 minutes later without changing the cuff position in order to calculate intra-measurement variation.

Statistical analysis

Each leg was considered a separate measure. Data are presented as mean and standard deviation, unless stated otherwise. Repeatability of duplicate oscillometric ABI measurement was evaluated using intraclass correlation coefficient calculated from one-way random effect model of ANOVA. Pearson's correlation coefficient was used to estimate association of the two techniques. Agreement between Doppler

TABLE I.—*Population characteristics.*

Variables	Mean±SD
Age (y)	54.29±13.77
Height (cm)	170.40±9.28
Weight (kg)	81.20±17.48
Waist (cm)	95.30±14.42
Hip (cm)	108.74±10.01
Cholesterol (mmol/L)	5.15±1.02
HDL-cholesterol (mmol/L)	1.44±0.38
LDL-cholesterol (mmol/L)	3.05±0.91
Glucose (mmol/L)	5.47±1.48
SBP (mmHg)	127.63±17.22
DBP (mmHg)	70.00±10.26
Heart rate (bpm)	80.30±9.38
Doppler ABI	1.16±0.11
BOSO ABI	1.06±0.09

HDL: high-density lipoprotein; LDL: low-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; ABI: ankle-brachial index; Doppler ABI: ABI using a Doppler device; BOSO ABI: ABI using an automatic oscillometric device.

TABLE II.—*Sex distribution and concomitant disease of the examined population.*

Variables	Number (%)
Sex (male)	393 (46.8%)
CHD	47 (5.6%)
DM	78 (9.3%)
HT	383 (45.6%)
HLP	608 (72.5%)
Stroke or TIA	19 (2.3%)
Claudications	6 (0.75%)
Doppler PAD	14 (1.7%)
Oscillometric PAD	27 (3.2%)

CHD: coronary heart disease; DM: diabetes mellitus; HT: arterial hypertension; HLP: hyperlipoproteinemia; TIA: transient ischemic attack.

and oscillometric ABI measurements, ankle and brachial systolic blood pressures, was assessed as proposed by Bland-Altman.[18] A correlation analysis between the difference of the two methods and mean ABI was performed to assess the association between these two parameters. Sensitivity, specificity, positive and negative predictive values of the BOSO ABI to detect ABI <0.9 were determined by the usual formula, taking the Doppler method as the gold standard. Calculations were done using SPSS 16 (Chicago, IL, USA). A P value of <0.05 was considered significant.

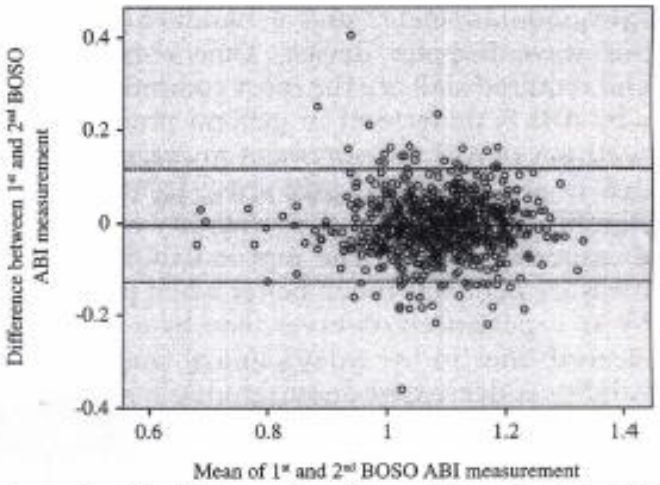

Figure 1.—Bland-Altman plot of repeated oscillometric ABI measurements. The plot is showing good reproducibility of the BOSO ABI device.

Results

Of the 930 patients examined in the district of Pilsen City, data on oscillometric ABI measurements were unavailable in 72 patients, Doppler ABI readings were lacking in four patients, and both oscillometric and Doppler ABI measurements were lacking in 15 patients, resulting in a total of 839 patients with complete data. The reason for lacking data was the high patient load on a particular day, not allowing us to examine everybody (N.=90), or venous ulcers in one patient. Characteristics of the study population are presented in Tables I, II.

The mean difference between duplicate ABI measurements for the BOSO ABI was not significantly different from zero (-0.006), with 95% limits of agreement ranging from -0.13 to 0.12 (Figure 1). The coefficient of repeatability was 0.12 and intraclass correlation coefficient of repeated measure 0.75 (95% confidence interval 0.72-0.78).

Mean difference between Doppler and oscillometric right arm systolic blood pressure was -5 mmHg, with 95% limits of agreement ranging from -24.9 to 14.9 mmHg. The mean difference between Doppler and oscillometric right leg systolic blood pressure was 4.8 mmHg (95% limits of agreement from -20.2 to 29.87) and 5.5 (95% limits of agreement from -20.5 to 31.1) for the left leg (data not shown).

There was an association between the two

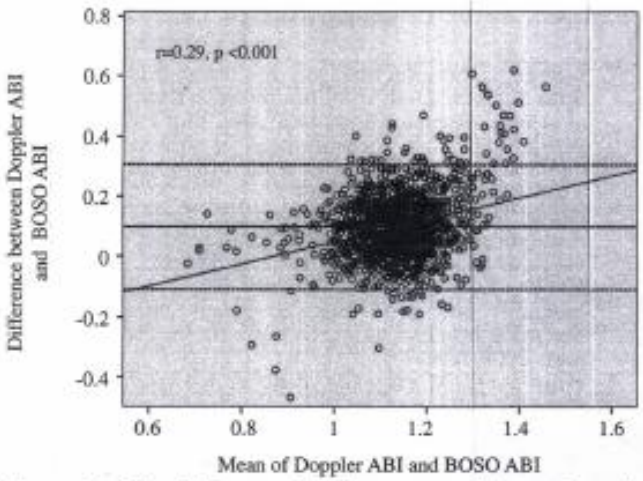

Figure 2.—Bland-Altman plot between oscillometric and Doppler ABI measurement. The plot illustrates weak agreement between oscillometric and Doppler methods of ABI measurement. The difference between Doppler and the BOSO ABI increases with increasing mean ABI.

methods of ABI measurement. A test of trends revealed a correlation coefficient of 0.45, P<0.001. The mean difference between Doppler and oscillometric method was 0.1±0.11 (95% limits of agreement from -0.11 to 0.30) (Figure 2). The difference between methods increased significantly with increasing mean ABI (r=0.29, P<0.001). Considering Doppler the gold standard, automated oscillometric measurement had a 76.7% sensitivity, 97.6% specificity, and 33.3% positive and 99.6% negative predictive values in diagnosing ABI <0.9.

Discussion

Peripheral arterial disease is an underdiagnosed and undertreated condition associated with high cardiovascular morbidity and mortality. Screening for PAD in everyday practice could identify asymptomatic individuals at high cardiovascular risk. Experts have proposed that ABI is the most effective, accurate, and practical method for diagnosing peripheral arterial disease. However ankle brachial index measurement using a handheld Doppler is not feasible in general practice due to the technical skills required and time consumption. Recommendation to measure ABI for cardiovascular risk stratification will lead to increased utilization of this test by less experienced observers, thus decreasing the reliability of measurement. These problems have led to the development of automatic oscillometric devices.

In our study we compared a novel oscillometric device to the standard Doppler device in an epidemiological setting. The advantage of the BOSO ABI compared with other oscillometric devices is its capability to measure blood pressure on all 4 limbs at a time, thus preventing blood pressure fluctuation between measurements.

Results of the present study demonstrate a weak agreement between the BOSO ABI and Doppler technique of ABI measurement. The width of the 95% confidence interval spans from low to normal ABI. Unequal distribution of the ABI difference on the Bland-Altman plot shows that the oscillometric method overestimates low ABI while underestimates high ABI. On the other hand, the oscillometric technique had a very high negative predictive value in excluding patients with a low ABI (ABI <0.9). That means that the BOSO ABI can be used in primary care as a screening tool for PAD with subsequent confirmation of the diagnosis of PAD by an experienced angiologist with Doppler or other techniques.

The difference observed between Doppler and oscillometric ABI measurement could be partially explained by the mechanism underlying oscillometric blood pressure measurement. Oscillometric systolic blood pressure is calculated on the basis of mean arterial pressure and oscillations dependent upon other factors of which arterial stiffness is the most important one.[19] Thus different levels of ankle arterial stiffness could differently influence oscillometric blood pressure.

In the literature, there are limited and inconsistent data on the agreement between Doppler and oscillometric ABI measurement. Most studies in agreement with our results did not find good agreement between oscillometric and Doppler ABI measurement.[20-22] Some studies concluded good accuracy of oscillometric ABI measurement.[23, 24] In other inappropriate statistical methods, such as correlation analysis, were used to examine agreement between methods, thus not allowing us to draw any conclusions from them.[25-27] Similarly to our observation, a high negative predictive value of oscillometric ABI method in determining ABI<0.9 was reported.[23, 28, 29]

Until now there was only one epidemiological

study comparing oscillometric, Doppler, and auscultatory techniques of ABI measurement.[16] In 946 subjects, mean ABI values were significantly higher on Doppler than auscultatory measurement, with intermediate levels on oscillometric determination. Similarly to our results, the difference between techniques was not homogeneously distributed across the range of ABI values. The differences between Dopple and oscillometric ABI increased with higher ABI values (r=0.21, P<0.0001). In our study, the correlation coefficient was 0.29 (P<0.001). Increasing difference between Doppler and oscillometric methods with increasing mean ABI also noted Beckaman *et al.*

Limitations of the study

Limitations of the study have been due to its epidemiological setting. Some justifications should have been done given the large sample size. Systolic blood pressure was measured only in the right brachial artery. The right brachial artery was chosen because it was described to have a systematically higher blood pressure.[30] Because of the high patient load on some days not every patient was examined; however, the total number of individuals missing this examination was 90 (9.67% of the total population examined in Pilsen City district). On the other hand, the epidemiological setting allowed us to calculate the prevalence of PAD in the Czech population, important for exact estimations of positive and negative predictive values.

Conclusions

According to our results performed in a random sample of the Czech population, automatic oscillometric ABI measurement with a novel BOSO ABI device cannot be used interchangeably for standard Doppler ABI measurement in order to diagnose PAD. However, its high negative predictive value allows using it as a screening tool for PAD, where one of the main objectives is to rule out disease. Minimal skill and time required makes the BOSO ABI a promising screening tool for general practice. The better diagnostic potential of PAD in primary care would help identify patients at high cardiovascular risk, who are otherwise asymptomatic.

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6.2 Srovnání vlivu kardiovaskulárních rizikových faktorů na tuhost aorty a tepen dolních končetin

Zatímco faktory ovlivňující rychlost pulzové vlny v aortě (aPWV) jsou dobře známy, málo je známo o faktorech ovlivňujících rychlost pulzové vlny v tepnách dolních končetin (lePWV). Na rozdíl od zvýšené tuhosti aorty není zvýšená tuhost tepen dolních končetin spojena s vyšším kardiovaskulárním rizikem (Pannier et al., 2005), ale omezuje průtok krve v dolních končetinách (Suzuki et al., 2001, Taniwaki et al., 2001, Tillin et al., 2007), a je spojena se zvýšenou hmotností levé komory (Ix et al.). Cílem této studie bylo porovnat vliv kardiovaskulárních rizikových faktorů na aPWV a lePWV.

Metodika

Pomocí přístroje SphygmoCor (AtCor Medical Ltd, West Ryde, New South Wales, Australia) jsme změřili karoticko-femorální (aPWV) a femoro-tibiální (lePWV) rychlost šíření pulzové vlny ve skupině 911 osob (průměrný věk 54 ± 13 let, 47 % mužů) ze studie Czech post-MONICA z okresu Plzeň.

Výsledky

Věk měl velký vliv na aPWV, ale pouze málo ovlivňoval lePWV. Po adjustaci na další proměnné byly hypertenze, diabetes, chronické onemocnění ledvin a dyslipidemie pozitivně a významně spojeny s tuhostí aorty, avšak pouze hypertenze měla významný vliv na tuhost tepen dolních končetin. Zvýšený kotníkový systolický krevní tlak byl asociován se zvýšenou aPWV nezávisle na brachiálním krevním tlaku. Kotníkový systolický krevní tlak byl asociován s aPWV více než s lePWV. Osoby s indexem kotník-paže pod 1,0 měli vyšší aPWV a nižší lePWV ve srovnání s jedinci s normálním indexem kotník-paže.

Diskuse

V naší práci jsme ukázali, že (1) věk a kardiovaskulární rizikové faktory jako hypertenze, diabetes, dyslipidemie a chronické onemocnění ledvin mají významný vliv na aortální tuhost, přičemž pouze věk a hypertenze mají významný vliv na tuhost tepen

dolních končetin; (2) abdominální obezita zvyšuje aPWV, zatímco zvýšený obvod boků je asociován se sníženou lePWV; (3) zvýšený kotníkový systolický tlak není asociován pouze se zvýšenou tuhostí tepen dolních končetin, ale i se zvýšenou tuhostí aorty; (3) u osob s nízkým poměrem kotník-paže je tuhost tepen dolních končetin falešně podhodnocena.

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ORIGINAL ARTICLE

Lower-extremity arterial stiffness *vs.* aortic stiffness in the general population

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While determinants of aortic pulse wave velocity (aPWV) are well known, much less is known about factors affecting lower-extremity pulse wave velocity (lePWV). Unlike aPWV, increased lePWV does not predict cardiovascular risk, but limits lower-extremity blood flow and is associated with increased left ventricular mass. The aim of this study was to compare the effect of cardiovascular risk factors on aPWV and lePWV. A total of 911 individuals from the Czech post-MONICA study (a randomly selected 1% representative population sample, mean age 54 ± 13.5 years, 47% men) were examined. Pulse wave velocity was measured using the SphygmoCor device. Aging had a large effect on aPWV, but only a small effect on lePWV. After adjustment for covariates, we observed that hypertension, diabetes, chronic kidney disease and dyslipidemia were positively and significantly associated with aPWV. However, only hypertension had a significant effect on lePWV. Increased ankle systolic blood pressure was associated with increased aPWV independently of brachial blood pressure. Ankle systolic blood pressure was more closely related to aPWV than lePWV. Subjects with an ankle-brachial index <1.0 had higher aPWV and lower lePWV compared with individuals with a normal ankle-brachial index. Lower-extremity arterial stiffness is affected by age and cardiovascular risk factors to a lesser extent than aortic stiffness. Increased ankle systolic blood pressure is linked not only to increased lower-extremity arterial stiffness, but also increased aortic stiffness. In subjects with a low ankle-brachial index, lower-extremity arterial stiffness is spuriously decreased.
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Keywords: ankle blood pressure; arterial stiffness; general population; peripheral arterial disease; pulse wave velocity

INTRODUCTION

Aortic pulse wave velocity (aPWV) as a measure of aortic stiffness is an independent predictive factor for all-cause and cardiovascular morbidity and mortality in patients with various levels of cardiovascular risk.[1] In contrast, stiffness of other arterial territories has a smaller or no ability to predict cardiovascular outcomes.[2–6] Indeed, carotid stiffness has been shown to predict cardiovascular events in patients with end-stage renal disease[2] and after renal transplantation.[3] However, in patients with manifest cardiovascular disease, carotid stiffness was not an independent risk factor for vascular events.[4] Brachial and femoro-tibial PWV were not predictors of cardiovascular mortality in patients with end-stage renal disease.[5] Furthermore, only carotid-femoral PWV was independently associated with coronary artery calcification, carotid and femoral plaques, whereas carotid-radial and femoro-tibial PWV were not.[6]

On the other hand, femoral artery stiffness was found to be closely associated with symptoms of lower limb peripheral arterial disease (PAD).[7] Furthermore, a negative correlation was shown between brachial-ankle PWV and blood flow in the popliteal artery,[8] and between femoral arterial stiffness and foot transcutaneous oxygen tension.[9] Lately, increased lower-extremity PWV (lePWV) determined by a high ankle-brachial index (ABI) was found to be linked to greater left ventricular (LV) mass through nonatherosclerotic pathways.[10]

Despite these findings suggesting the importance of lower-extremity arterial stiffness in lower-extremity blood flow and its association with LV hypertrophy, there have been only a few studies identifying determinants of lower-extremity arterial stiffness. Most of these studies determined lower-extremity arterial stiffness from local femoral arterial distensibility. Measurement of local vascular distensibility is often confounded by pressure most often measured at the brachial level and not locally, resulting in amplification-related errors. In addition, previous studies have reported the effect of lower-extremity peripheral arterial disease (PAD) on brachial-ankle PWV,

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but no study has determined the effect of lower-extremity arterial stenosis on lePWV.

The aim of the present study was to compare the effect of cardiovascular risk factors on lower-extremity and aortic stiffness. In order to determine the effect of lower-extremity peripheral arterial disease on lower-extremity arterial stiffness, lePWV was compared in patients with a low, normal and high ankle-brachial index.

METHODS

Study population

The Czech post-MONICA study is a population survey studying trends and determinants of cardiovascular risk factors in a random sample of the Czech population. Methods of the Czech post-MONICA study have been described elsewhere.[11] Our study included patients aged >25 years, residing in Pilsen district. The response rate in this district was 68%. A total of 911 patients (98% of patients examined in Pilsen district) had complete data on ABI and PWV. The study was approved by the local ethics committee of the Institute for Clinical and Experimental Medicine and Thomayer University Hospital, and was in accordance with the Declaration of Helsinki.

Hypertension was defined as systolic blood pressure (SBP) ⩾140 mm Hg and/or diastolic blood pressure (DBP) ⩾90 mm Hg, or current use of antihypertensive medication. Diabetes was defined as fasting plasma glucose ⩾7.0 mmol l^{-1} or use of oral antidiabetic drugs and/or insulin. Dyslipidemia was defined as total cholesterol ⩾5 mmol l^{-1} or high density lipoprotein-cholesterol <1 mmol l^{-1} in men and <1.2 mmol l^{-1} in women or use of lipid-lowering drugs. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) <60 ml min^{-1} per 1.73 m^2. Glomerular filtration rate was estimated using the simplified CKD-EPI formula as described by Levey.[12]

Measurement of large artery properties

Large artery properties were measured using the SphygmoCor device (AtCor Medical Ltd, West Ryde, New South Wales, Australia) in the recumbent position as reported before.[13] Aortic pulse wave velocity and lePWV were assessed according to recommendations.[14] Consecutive registrations of the pulse waves are ECG-gated and thus, the time shift (Δt) between the foot of wave at the first and second sites can be calculated. The distance between the two sites was measured on the body surface. To determine aPWV, we measured the distance from the jugular fossa to the pulsation of the femoral artery in the groin and subtracted the distance from the jugular fossa to carotid pulsation in order to obtain the traveled distance (D). The distance between the femoral artery and dorsal pedal/posterior tibial arteries was measured to calculate lePWV. PWV was calculated as D (m)/Δt (s).

Doppler ABI measurement

Details of ABI measurement are described in our previous paper.[15] Briefly, appropriately sized cuffs of a mercury sphygmomanometer (Baumanometer TM, WA Baum, New York, NY, USA) were placed proximal to the ankles and on the right arm. After a 5 min resting period, SBP was measured on the right brachial artery, right dorsal pedal and posterior tibial arteries, left dorsal pedal and tibial arteries (in this order) using a pocket Doppler device with an 8 MHz probe (DopplexmultiTM, Huntleigh, Cardiff, UK). All measurements were performed by two physicians experienced in ABI measurement. ABI was calculated separately for each leg by dividing the highest of the ankle systolic pressures by the brachial systolic pressure. The lower of the two leg ABI values was used in further analysis. Systolic blood pressure measured on the right posterior tibial artery was used for further analyses and is indicated as ankle blood pressure (aSBP). A cutoff value of 175 mm Hg was used to identify subjects with increased aSBP as reported earlier.[16]

Statistical analysis

Descriptive statistics are given as mean ± s.d., mean (95% CI) or frequency and percent. In the figures, error bars represent s.e.m. In order to determine the effect of age and gender on arterial stiffness, analysis of covariance with adjustment for mean arterial pressure (MAP) was performed while subdividing individuals into quintiles of age. The effect of cardiovascular risk factors on arterial stiffness was determined by analysis of covariance with adjustment for age, gender and MAP. Partial eta-squared (η^2_p) is reported, indicating how much variability of the dependent variable can be predicted by the independent variable. The effect size was considered large for η^2_p >0.30. To determine the effect of PAD on arterial stiffness, participants were divided into three groups on the basis of their ABI: low (ABI<1.0), normal (ABI = 1–1.4), and high (ABI⩾1.4). Arterial properties between these groups were compared using one-way analysis of variance with Turkey's *post-hoc* test. Differences between groups were reassessed after adjustment for age, gender and MAP. Determinants of aPWV, lePWV and aSBP were assessed by multiple linear regression analysis. Variables significantly associated with parameters of arterial stiffness in univariate analyses were included into the multiple regression analyses. Standardized values of the mean and the systolic blood pressure were used to decrease colinearity between parameters. We considered the stability of the regression model to be disturbed by multi-colinearity if the tolerance was <0.1. Standardized beta is reported ($ß_S$). A $ß_S$ of 0.1 indicates that when the independent variable increases by 1 s.d., the dependent variable increases by 0.1 s.d. All calculations were performed using SPSS 16 software (SPSS, Chicago, IL, USA). A two-sided P-value <0.05 was considered to be statistically significant.

RESULTS

Study population characteristics

Characteristics of the study population of 911 individuals (430 male and 481 female; mean age of 54.1 ± 13.49 years), with complete data, are provided in Table 1.

Effect of age and gender on aortic and lower-extremity pulse wave velocities

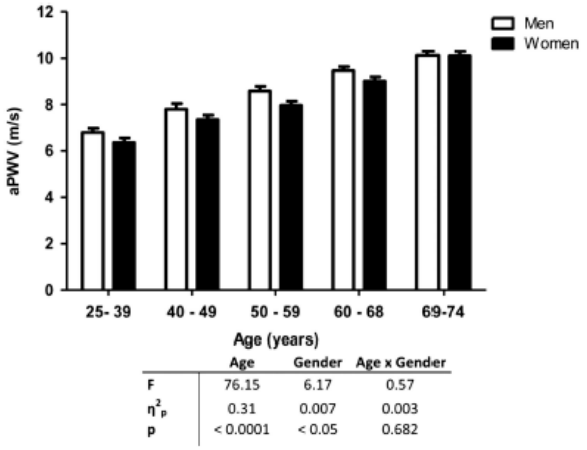
Aortic pulse wave velocity increased with age (P<0.001) both in men and women, with the mean aPWV higher in men (Figure 1). Partial eta-squared representing explained variability was high for age (η^2_p = 0.32), while there was only a minor effect of gender (η^2_p = 0.01). No interaction between age and gender was found (P = 0.68).

Mean lower-extremity pulse wave velocity was higher in men than in women and showed a significant increase with age. There was a

Table 1 Study population characteristics

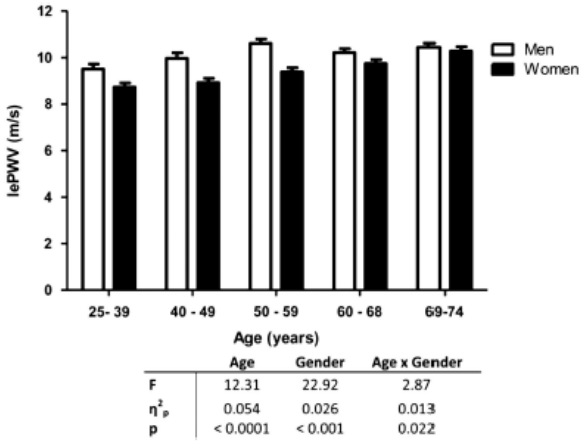
SBP, mm Hg	127.70 ± 17.15
DBP, mm Hg	69.48 ± 10.81
MAP, mm Hg	92.77 ± 9.81
lePWV, m s^{-1}	9.77 ± 1.81
aPWV, m s^{-1}	8.42 ± 2.34
eGFR, ml min^{-1} per 1.73 m^2	75.08 ± 12.46
Total cholesterol, mmol l^{-1}	5.16 ± 1.01
Triglycerides, mmol l^{-1}	1.51 ± 1.03
HDL-cholesterol, mmol l^{-1}	1.43 ± 0.42
LDL cholesterol, mmol l^{-1}	2.92 ± 1.28
Fasting plasma glucose, mmol l^{-1}	5.39 ± 1.23
CHD, *n* (%)	46 (5%)
Hypertension, *n* (%)	420 (46%)
Diabetes, *n* (%)	70 (8%)
Dyslipidemia, *n* (%)	640 (71%)
Current smokers, *n* (%)	254 (28%)
Low ABI, *n* (%)	28 (3%)
High ABI, *n* (%)	23 (2.5%)

Abbreviations: ABI, ankle-brachial index; aPWV, aortic pulse wave velocity; CHD, coronary heart disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, lowdensity lipoprotein; lePWV, lower-extremity pulse wave velocity; MAP, mean arterial pressure; SBP, brachial systolic blood pressure.
Values are presented as mean ± standard deviation or frequency (percent).



	Age	Gender	Age x Gender
F	76.15	6.17	0.57
η^2_p	0.31	0.007	0.003
p	< 0.0001	< 0.05	0.682

Figure 1 Effect of age and gender on aortic PWV (aPWV). Data adjusted for mean arterial pressure, height and weight.



	Age	Gender	Age x Gender
F	12.31	22.92	2.87
η^2_p	0.054	0.026	0.013
p	< 0.0001	< 0.001	0.022

Figure 2 Effect of age and gender on lower-extremity PWV (lePWV). Data adjusted for mean arterial pressure, height and weight.

significant age–gender interaction. While, in women, there was a linear increase in lePWV with increasing age ($P<0.001$ for linear term), in men there was only a minor change after 59 years of age. Partial eta squared was higher for age ($\eta^2_p=0.054$) than for gender ($\eta^2_p=0.026$), with only a minor effect of age–gender interaction ($\eta^2_p=0.013$) (Figure 2). When individuals with low ABI were excluded from the analysis of age and gender effect on lePWV, the age–gender interaction was no longer significant ($P=0.12$), while the η^2_p for age and gender increased.

Effect of cardiovascular risk factors on aPWV and lePWV

Table 2 summarizes the effect of different cardiovascular risk factors on aPWV and lePWV. In unadjusted analyses, subjects with hypertension, diabetes and dyslipidemia had higher aPWV. The effect of these risk factors on aPWV remained unchanged after adjustment for covariates. Lower-extremity arterial stiffness was higher in individuals with hypertension and dyslipidemia. However, after adjustment, only hypertension remained associated with elevated lePWV. The effect of cardiovascular risk factors on lePWV did not change significantly after excluding individuals with low ABI.

Association of aPWV and lePWV with lower-extremity peripheral arterial disease

Aortic pulse wave velocity was higher in subjects with low and high ABI compared with the normal ABI group (high ABI, 11.1 ± 2.8 *vs.* 8.3 ± 2.3, $P<0.0001$; low ABI, 10.8 ± 2.5 *vs.* 8.3 ± 2.3, $P<0.0001$, respectively). There was no difference in aPWV between patients with low and high ABI ($P=0.86$). The elevation of aPWV in both extreme ABI groups remained unchanged after adjustment for age, gender and MAP (Figure 3a).

There was a linear increase in lePWV with increasing ABI ($P<0.001$ for linear trend). Lower-extremity PWV was lowest in individuals in the low ABI group (8.82 ± 1.85), intermediate in individuals with normal ABI (9.78 ± 1.81) and highest in individuals with high ABI (10.98 ± 1.28). In a model adjusted for age, gender and MAP, individuals with low ABI had lower lePWV compared with the normal ABI group (8.23 (7.57–8.89) *vs.* 9.81 (9.70–9.92), $P<0.0001$) and the high ABI group (8.23 (7.57–8.89) *vs.* 10.24 (9.55–10.93, $P<0.0001$), while there was no difference between the normal and high ABI groups (Figure 3b).

Determinants of aPWV and lePWV

In univariate analyses, the following parameters were associated with aPWV: age, MAP, SBP, DBP, serum cholesterol, waist circumference, triglycerides, glucose, creatinine level, eGFR, waist circumference, lePWV, heart rate and aSBP. In a multivariate model of linear regression (Table 3), age had the largest effect on aPWV, explaining 36% of the total variance. Among the conventional cardiovascular risk factors, MAP, SBP, abdominal obesity and CKD were independently associated with aortic stiffness. Lower-extremity SBP was also associated with aPWV independently of brachial SBP and other cardiovascular risk factors. Individuals with aSBP >175 mm Hg had higher aPWV at all levels of brachial blood pressure (Figure 4), which suggests that ankle systolic blood pressure is associated with aortic stiffness independently of brachial systolic blood pressure. In the receiver operating characteristic analysis (area under the curve $=0.71\pm0.02$, $P<0.001$), after excluding individuals with low ABI, aSBP >175 mm Hg had a sensitivity of 58% and a specificity of 84% to detect subjects with aPWV $>10\,m\,s^{-1}$.

In univariate analyses, the following parameters were associated with lePWV: SBP, DBP, MAP, aSBP, age, weight, hip circumference, eGFR, serum creatinine, aPWV and glucose levels. In the multivariate model of linear regression (Table 3), aSBP, age, gender, MAP, low ABI and hip circumference were independent predictors of lePWV.

In multiple regression analyses, after excluding individuals with low ABI, ankle blood pressure was determined by brachial SBP, MAP, aPWV, height, age and lePWV. Aortic stiffness ($ß_S=0.11$, $P<0.001$, $R^2=0.02$) had a larger effect on ankle blood pressure than lePWV ($ß_S=0.06$, $P<0.001$, $R^2=0.004$).

DISCUSSION

In this study, we compared the determinants of aortic stiffness with those of lower-extremity arterial stiffness. We observed that the effect of cardiovascular risk factors on arterial stiffness differed between these two arterial territories. The principal findings of our study are as follows: (1) age and cardiovascular risk factors such as hypertension, diabetes, dyslipidemia and chronic kidney disease affect aortic stiffness, while only age and hypertension have a significant effect on lower-extremity stiffness, (2) abdominal obesity increases aortic

Q3 **Table 2 Effect of cardiovascular risk factors on aortic and lower-extremity PWV**

	Unadjusted aPWV	*Adjusted aPWV*	*Unadjusted lePWV*	*Adjusted lePWV*
Hypertension[a]				
Yes	9.70 (9.47–9.92)	8.99 (8.81–9.18)	10.22 (10.04–10.41)	9.95 (9.77–10.13)
No	7.32 (7.17–7.46)	7.91 (7.73–8.09)	9.39 (9.24–9.54)	9.63 (9.47–9.79)
P	**<0.001**	**<0.001**	**<0.001**	**0.018**
η^2_p	0.253	0.071	0.05	0.006
Diabetes[b]				
Yes	10.43 (9.78–11.08)	9.18 (8.76–9.60)	10.0 (9.51–10.49)	9.38 (8.95–9.80)
No	8.24 (8.09–8.39)	8.36 (8.25–8.48)	9.75 (9.62–9.87)	9.79 (9.69–9.91)
P	**<0.001**	**<0.001**	0.30	0.08
η^2_p	0.059	0.015	—	—
Dyslipidemia[b]				
Yes	8.74 (8.56–8.91)	8.53 (8.40–8.66)	9.89 (9.75–10.03)	9.87 (9.62–10.12)
No	7.61 (7.35–7.88)	8.03 (7.77–8.30)	9.47 (9.25–9.69)	9.87 (9.62–9.87)
P	**<0.001**	**<0.001**	**<0.001**	0.518
η^2_p	0.05	0.003	0.012	—
Current smoking[b]				
Yes	7.95 (7.68–8.22)	8.23 (7.99–8.47)	9.74 (9.49–9.99)	9.83 (9.62–9.88)
No	8.59 (8.24–8.79)	8.49 (8.36–8.62)	9.77 (9.54–10.01)	9.75 (9.60–10.06)
P	**<0.001**	0.06	0.98	0.53
η^2_p	**0.014**	—	—	—
Chronic kidney disease[b]				
Yes	10.38 (9.56–10.77)	9.19 (8.79–9.58)	9.97 (9.54–10.40)	9.55 (9.16–9.94)
No	8.25 (8.09–8.39)	8.35 (8.23–8.47)	9.75 (9.63–9.88)	9.79 (9.68–9.91)
P	**<0.001**	**<0.001**	0.35	0.23
η^2_p	0.064	0.017	—	—

Abbreviations: aPWV, aortic pulse wave velocity; lePWV, lower-extremity pulse wave velocity.
[a]Adjusted for age and gender.
[b]Adjusted for age, gender and mean arterial pressure.
Data are expressed as mean (95% CI).

stiffness, while a larger hip circumference is associated with lower-extremity stiffness, (3) increased ankle systolic blood pressure is associated with increased aortic stiffness independently of brachial systolic pressure and other cardiovascular risk factors, (4) lower-extremity arterial stiffness is spuriously decreased in individuals with lower-extremity PAD.

In our study, age had a major effect on aortic stiffness, but only a small effect on lower-extremity arterial stiffness. This may be due to the different histological structure of these arteries and a different effect of aging on these structures. In elastic arteries, aging leads to fragmentation and alteration of the elastic fiber network responsible for buffering function, while aging in the muscular arteries leads to changes in the extracellular matrix involving mainly collagen fibers, and to hypertrophy of vascular smooth muscle cells and the arterial wall, acting in the opposite direction on arterial stiffness.[17,18] Indeed, there is general agreement that aortic stiffness increases with age, but there are discrepant data on aging of the lower-extremity arteries. While, in some studies,[19,20] no increase in femoral artery stiffness with age was found, there was some increase in femoral[21] and lower limb arterial stiffness[22–24] in others. This discrepancy can be explained by the small effect of age on lePWV and different methods of arterial stiffness measurement.

We found hypertension to increase lower-extremity arterial stiffness. However, in other studies,[25,26] hypertension had no effect or it decreased brachial artery stiffness. Of note, the brachial artery is also less prone to atherosclerosis than major arteries in the lower extremities. This suggests that differences in muscular arteries do exist.

We found a significant gender difference in aPWV and lePWV that was independent of anthropometric parameters and blood pressure. The effect of gender on stiffness was small as evident from the small η^2_p. We found a significant age–gender interaction on lePWV that became non-significant after excluding individuals with PAD. This was probably due to the higher prevalence of men with PAD. The gender difference in lePWV observed in our study is in agreement with previous reports.[20,27,28]

In our study, abdominal obesity expressed as waist circumference was associated with increased aPWV. Waist circumference is closely associated with visceral fat mass. Increased intraabdominal fat is known to contribute to hyperglycemia and hyperinsulinemia due to increased secretion of free fatty acids. These factors are known to affect aortic stiffness. The closer association of waist circumference with visceral fat and cardiovascular risk factors than BMI[29] explains why waist circumference was associated with aPWV in multiple regression analysis, while BMI was not. Our finding is in agreement with previous reports[30,31] in which only waist circumference was independently associated with aortic stiffness, while BMI, hip circumference, fat mass, fat free mass and the waist/hip ratio were not. While waist circumference was associated with increased aPWV, we found increased hip circumference to be linked to lower lePWV.

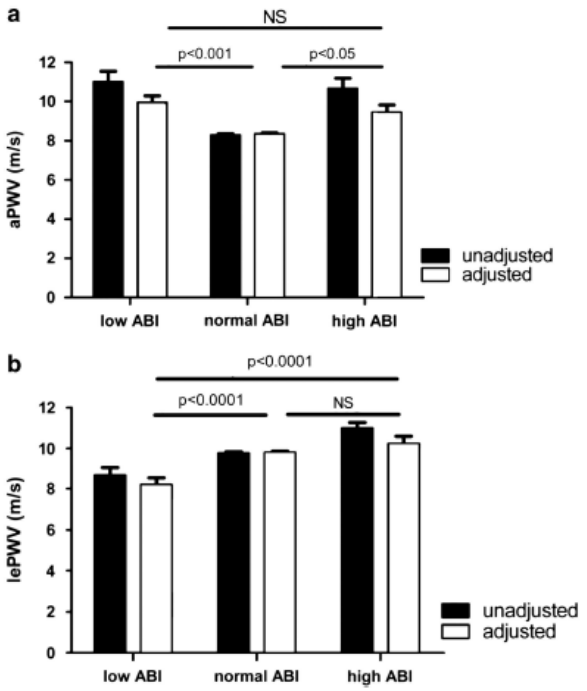


Figure 3 Association of ABI with aPWV (**a**) and lePWV (**b**). Data are shown before and after adjustments for age, gender and MAP. Significance values are for adjusted models, see text for *P*-values of unadjusted models. ABI, ankle-brachial index; aPWV, aortic pulse wave velocity; lePWV, lower-extremity pulse wave velocity; MAP, mean arterial pressure. A full color version of this figure is available at the *Hypertension Research* journal online.

Table 3 Multivariate stepwise analysis of the determinants of aPWV, lePWV and aSBP

	Standardized B	r^2	P
Aortic pulse wave velocity[a], $r^2 = 0.55$			
Age (years)	0.404	0.365	<0.001
MAP (mm Hg)	0.109	0.108	<0.001
Heart rate (beats per min)	0.184	0.031	<0.001
aSBP (mm Hg)	0.160	0.026	<0.001
Waist circumference (cm)	0.105	0.014	<0.001
bSBP (mm Hg)	0.137	0.010	<0.001
CKD	0.081	0.006	<0.001
Lower-extremity pulse wave velocity[a], $r^2 = 0.21$			
aSBP (mm Hg)	0.172	0.128	<0.001
Age (years)	0.181	0.022	<0.001
Gender (female)	−0.161	0.023	<0.001
MAP (mm Hg)	0.144	0.010	<0.001
Low ABI	−0.104	0.011	<0.01
Hip circumference (cm)	−0.081	0.006	<0.01
Ankle systolic blood pressure[a,b], $r^2 = 0.62$			
bSBP (mm Hg)	0.382	0.515	<0.001
MAP (mm Hg)	0.333	0.078	<0.001
aPWV ($m\,s^{-1}$)	0.114	0.018	<0.001
Height (cm)	0.071	0.003	<0.001
Age (years)	0.092	0.004	<0.001
lePWV ($m\,s^{-1}$)	0.063	0.004	<0.01

Abbreviations: ABI, ankle-brachial index; aSBP, ankle systolic blood pressure; aPWV, aortic pulse wave velocity; bSBP, brachial systolic blood pressure; CKD, chronic kidney disease; lePWV, lower-extremity pulse wave velocity; MAP, mean arterial pressure.
[a]Adjusted for antihypertensive and lipid-lowering therapy.
[b]Individuals with low ABI excluded.

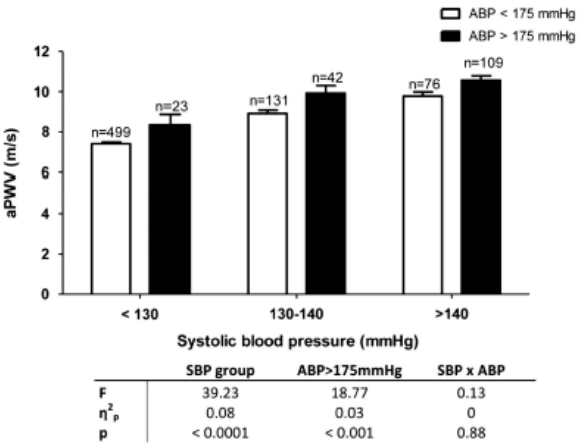


Figure 4 Effect of bSBP and aSBP on aortic pulse wave velocity. aSBP, ankle systolic blood pressure; aPWV, aortic pulse wave velocity; bSBP, brachial systolic blood pressure.

This finding is in agreement with the results of the Hoorn study, in which larger leg fat mass and leg lean mass were associated with lower peripheral arterial stiffness. This may be one of the explanations why increased hip circumference is associated with lower cardiovascular risk in population studies,[32] and why the gynoid type of obesity is less deleterious than the android one.

Another new finding is the association between aSBP and aPWV that was independent of cardiovascular risk factors including brachial SBP. Furthermore, we found aSBP to be more closely related to aortic stiffness than to lePWV. This suggests that aSBP is more a parameter of aortic stiffness than that of lower-extremity stiffness. Increased transmission of pulsatile energy to the periphery due to increased aortic stiffness may be the potential mechanism explaining association between aSBP and aPWV.[33] Increased pulsatile stress to the peripheral circulation due to aortic stiffening is caused by loss of buffering function of aorta and impedance mismatch loss between aorta and peripheral circulation. Normally, wave reflection occurs due to arterial stiffness mismatch between the aorta and large muscular arteries. Partial wave reflection protects microcirculation from the damaging effect of pulsatile energy. As aortic stiffness meets the stiffness of large muscular arteries, wave reflection is reduced and more pulsatile energy is transmitted to the periphery. Our results suggest that increased aSBP is linked to increased aortic stiffness and may be a parameter of increased pulsatile energy transmission to the periphery. To confirm this theory, energy waves in posterior tibial artery will have to be assessed in the future. The association between aSBP and aortic stiffness may explain the observed positive association between lower-extremity stiffness and LV mass, which is independent of subclinical atherosclerosis.[10]

The independent predictive role of the aSBP in cardiovascular prediction was described previously. In a population study,[16] aSBP >175 mm Hg was an independent predictor of total and

cardiovascular mortality in asymptomatic individuals independently of all traditional cardiovascular risk factors. In another study, aSBP improved the prediction of cardiovascular events independently of classical risk factors.[34] Further studies will be needed to assess the predictive role of ankle SBP in cardiovascular prediction. The advantage of the aSBP examination is that it is fast, non-invasive, feasible and widely available.

We found decreased lePWV in individuals with lower-extremity PAD (low ABI group). We think that this is an artifact due to significant stenosis. The explanation of this phenomenon can be the blood pressure decrease behind stenosis. Distending pressure is one of the major determinants of arterial stiffness. Moreover, pressure waveform changes have been reported in patients with PAD. Among other things, delay in the foot of the waveform has been reported in patients with PAD compared with normal subjects.[35] It is the foot of the pulse wave that is commonly used for time delay calculation in order to estimate PWV. Another explanation is the increase in the distance traveled due to collateral circulation. The effect of PAD on brachial-ankle PWV (baPWV) was described previously. Yokoyama *et al.*[36] reported baPWV reduction in a leg affected with PAD compared with the non-affected leg. Moreover, baPWV increased following successful stenosis dilatation. In another study, an ABI of 0.95 was calculated to be the cutoff value for diminished accuracy of baPWV.[37]

In the current study, we estimated the aortic length by subtracting the jugular fossa to the carotid pulsation distance from the jugular fossa to the femoral artery pulsation side. This method is known to underestimate the true aortic stiffness. The current consensus for aortic stiffness measurement is to use 80% of the direct distance between carotid and femoral measurement sides with the cutoff value of $10\,m\,s^{-1}$.[14] However, this has no effect on the strength of association with cardiovascular risk factors and the conclusions of our study.

Our results suggest that conventional cardiovascular risk factors, except for hypertension, have only a small effect on lower-extremity arterial stiffness. The effect of aortic stiffness on peripheral vasculature may be explained by increased pulsatile energy transmission to the periphery due to increased aortic stiffness. Increased ankle systolic blood pressure may be a parameter of increased pulsatile energy transmission to the periphery. Further research is needed to evaluate energy waves in lower-extremity arteries and to confirm the association between increased ankle blood pressure and microcirculation damage.

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6.3 Vliv přidání tuhosti tepen dolních končetin k tuhosti aorty na asociaci se subklinickým orgánovým poškozením

Aortální tuhost je nezávislým prediktorem kardiovaskulární morbidity a mortality (Laurent, Boutouyrie, 2007), zatímco tuhost ostatních tepen má malou nebo žádnou schopnost predikovat kardiovaskulární riziko (Blacher et al., 1998, Barenbrock et al., 2002, Dijk et al., 2005, Pannier et al., 2005, Tillin et al., 2007). Rozdílná prediktivní hodnota různých arteriálních oblastí může být podmíněna rozdíly v histologickém složení (Laurent, 1995, Laurent et al., 2005). Zatímco v Evropě a USA se používá parametr aortální tuhosti stanovený mezi karotickou a femorální tepnou (karoticko-femorální rychlost šíření pulzové vlny – cfPWV), v Japonsku a Asii stanovují rychlost šíření pulzové vlny (pulse wave velocity - PWV) mezi brachiální tepnou a kotníkem (brachiálno-kotníková rychlost šíření pulzové vlny – baPWV). Tento parametr arteriální tuhosti kombinuje aortální tuhost s tuhostí periferních muskulárních tepen, které mají omezenou prediktivní hodnotu. V současné době existují omezené poznatky o vlivu přidání arteriální tuhosti muskulárních tepen k aortální tuhosti na vztah s kardiovaskulárními rizikovými faktory a subklinickým orgánovým poškozením. Novým parametrem arteriální tuhosti, jehož výhodou je nezávislost na krevním tlaku (Shirai et al., 2011), je parametr tuhosti BETA, který lze odvodit z PWV [$BETA = ln\ (systolický / diastolický\ tlak) \times 2\ viskozita\ krve / tlaková\ amplituda \times PWV^2$). Cílem naší studie bylo porovnat různé parametry cévní tuhosti v obecné populaci.

Metodika Ve skupině 809 osob ze studie Czech post-MONICA (náhodně vybraný 1% reprezentativní vzorek populace ve věku 54 ± 13 let, 47 % mužů) jsme porovnávali sílu asociace cfPWV, karoticko-kotníkové PWV (caPWV) a parametru tuhosti BETA odvozeného z PWV (cfBETA a caBETA) s kardiovaskulárními rizikovými faktory, parametry subklinického orgánového poškození a manifestním kardiovaskulárním onemocněním. Arteriální tuhost jsme stanovovali pomocí přístroje SphygmoCor.

Výsledky Karoticko-femorální PWV a caPWV byly podobně a významně spojeny s krevním tlakem a hladinou glukózy, zatímco cfPWV byl silněji spojen s věkem, hladinou cholesterolu a glomerulární filtrací a caPWV s hypertrofií levé komory stanovené pomocí indexu Sokolow-Lyon. Parametr tuhosti BETA odvozený z cfPWV i caPWV byl méně závislý na krevním tlaku a vykazoval užší vztah k přítomnosti ischemické choroby srdeční ve srovnání s cfPWV a caPWV (cfBETA vs cfPWV 0,731

± 0,03 vs. 0,04 ± 0,714, p <0,05; caBETA vs caPWV 0,740 ± 0,03 vs. 0,04 ± 0,711, p <0,05).

Diskuse Naše výsledky ukazují, že přidání tuhosti tepen dolních končetin k aortální tuhosti má vliv na vztah ke kardiovaskulárním rizikovým faktorům, zatímco neovlivňuje vztah k manifestním kardiovaskulárním onemocněním. Karoticko-femorální PWV je více asociována s renálními funkcemi, zatímco caPWV vykazuje vyšší asociaci s hypertrofií levé komory. Tento poznatek je v souladu s výsledkem studie Yu *et al* (Yu et al., 2008*),* kteří ukázali, že baPWV je asociována s hmotností levé komory a její systolickou funkcí více než aortální PWV. To naznačuje, že periferní muskulární tepny ovlivňují interakci mezi levou komorou a cévním systémem nezávisle na velkých elastických tepnách. Ve studii jsme dále ukázali, že BETA transformace PWV snižuje závislost PWV na krevním tlaku a může zvýšit jeho nezávislou prediktivní schopnost. To naznačuje, že zvýšení arteriální tuhosti vlivem strukturálních změn cévní stěny je spojeno s vyšším rizikem než zvýšení cévní tuhosti způsobené zvýšeným krevním tlakem.

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Arterial stiffness parameters: How do they differ?

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Arterial stiffness parameters: How do they differ?

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ABSTRACT

Background: Carotid-femoral pulse wave velocity (PWV), as a parameter of aortic stiffness, is an established marker of cardiovascular risk. There has been increasing use of arterial stiffness parameters combining aortic and muscular stiffness or a parameter derived from PWV – the stiffness index beta (BETA = $ln(systolic/diastolic\ pressure) \times 2\ blood\ viscosity/pulse\ pressure \times PWV^2$). The aim of this study was to compare different arterial stiffness parameters in a general population random sample.

Methods and results: In 809 individuals from the Czech post-MONICA study (aged 54 ± 13.5 years, 47% men), we compared the association of carotid-femoral PWV (cfPWV), carotid-ankle PWV (caPWV), and BETA with cardiovascular risk factors, parameters of subclinical organ damage, and presence of manifest cardiovascular disease.

Both cfPWV and caPWV were similarly associated with blood pressure and glucose level, while cfPWV was more strongly associated with age, cholesterol level and glomerular filtration rate whereas caPWV with Sokolow-Lyon index. BETA derived from cfPWV and caPWV was less dependent on blood pressure, while it showed a closer association with coronary heart disease presence, as compared to cfPWV and caPWV.

Conclusions: Addition of lower extremity to aortic stiffness has an effect on the association with cardiovascular risk factors while having no effect on the association with manifest cardiovascular disease. Beta transformation of PWV decreases its dependence on blood pressure and may increase its power in cardiovascular risk prediction.

1. Introduction

Pulse wave velocity (PWV) measured between the carotid and femoral arteries (cfPWV) as a measure of aortic stiffness has been shown to be an independent predictive factor for all-cause and cardiovascular morbidity and mortality in patients with various levels of cardiovascular risk [1]. In contrast, stiffness of other arterial territories has a smaller or no ability to predict cardiovascular outcomes [2–6]. Indeed, carotid stiffness has been shown to predict cardiovascular events in patients with end-stage renal disease [2] and after renal transplantation [3], while in a large cohort of patients with manifest cardiovascular disease, carotid stiffness was not an independent risk factor for vascular events [4]. Brachial and femoro-tibial PWV were not predictors of cardiovascular mortality in patients with end-stage renal disease [5]. Furthermore, only carotid-femoral PWV was independently associated with coronary artery calcification, carotid and femoral plaques in men with and without coronary artery disease, whereas carotid-radial and femoro-tibial PWV were not [6].

Difference in predictive value of these arterial territories may be explained by different histological structure and different effect of aging and risk factors on these structures. In elastic arteries, aging and risk factors lead to fragmentation and alteration of the elastic fiber network responsible for buffering function. On the other hand, in the muscular arteries these risk factors lead to changes in the extracellular matrix involving mainly collagen fibers, and to hypertrophy of vascular smooth muscle cells and the arterial wall, acting in the opposite direction on arterial stiffness [7,8].

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While the parameter commonly used in Europe and USA is the carotid-femoral PWV (measured between carotid and femoral artery), in Japan and other East Asian countries, arterial stiffness has been measured between the brachial artery and ankle—the so called brachial-ankle PWV index (baPWV). This arterial stiffness parameter reflects the properties of peripheral muscular arteries, but it has been shown to be more influenced by aortic stiffness [9,10]. The effect of addition of muscular arterial stiffness to aortic stiffness on the association with cardiovascular risk factors, parameters of subclinical organ damage and in cardiovascular risk prediction has not been fully evaluated. To date, there has been only one large-scale study comparing baPWV and cfPWV [11]. In this cross-sectional study, brachial-ankle pulse wave velocity was shown to exhibit an extent of associations with cardiovascular disease risk factors and clinical events similar to that of cfPWV.

Recently, a new parameter of regional arterial stiffness derived from the arterial stiffness parameter BETA, called cardio-ankle vascular index (CAVI) has been proposed. BETA can be calculated from PWV using the equation $BETA = ln(SBP/DBP) \times 2\varsigma/PP \times PWV^2$ [12], where the (ln) denotes natural logarithm, (SBP) systolic blood pressure, (DBP) diastolic blood pressure, (PP) pulse pressure, (ς) blood viscosity and (PWV) pulse wave velocity. In order to match BETA and PWV, CAVI was introduced using scale conversion constants from BETA ($CAVI = a[ln(SBP/DBP) \times 2\varsigma/PP \times PWV^2] + b$) [13]. The proposed advantage of this new stiffness parameter over PWV is its independence from blood pressure [14]. CAVI is suggested to better reflect structural changes of the arterial wall independently of distending blood pressure. However, the predictive role of this new arterial stiffness parameter has never been tested against PWV.

The purpose of our study was (1) to assess the effect of addition of muscular arterial stiffness to aortic stiffness on association with cardiovascular risk factors and subclinical organ damage as compared to aortic stiffness alone and (2) to compare the new stiffness parameter BETA of the carotid-femoral and carotid-ankle regions with the carotid-femoral and carotid-ankle PWV, respectively.

2. Methods

2.1. Study population

The Czech post-MONICA study is a population survey studying trends and determinants of cardiovascular risk factors in a random sample of the Czech population. Methods of the Czech post-MONICA study have been described elsewhere [15]. Our study included patients aged over 25 years resident in Pilsen district. The response rate in this district was 68%. A total of 834 individuals had complete data on carotid-femoral, femoral-ankle PWV and parameters of subclinical organ damage. Based on previous reports [16–18] that lower extremity peripheral arterial disease artificially decreases lower extremity arterial stiffness, we excluded 25 subjects with an ankle-brachial index (ABI) below 1.0. This left us with 809 patients. The study was approved by the local ethics committee of the Institute for Clinical and Experimental Medicine and Thomayer Hospital, Prague, Czech Republic, and was in accordance with the Declaration of Helsinki. All participants provided informed consent.

2.2. Laboratory analysis

All laboratory analyses were performed centrally in the Institute for Clinical and Experimental Medicine, Prague, Czech Republic. Lipid analyses were performed in the Lipid Laboratory of the Institute for Clinical and Experimental Medicine using a fully automated enzymatic method (Cobas MIRA S analyzer) with enzymatic kits by the same manufacturer. Glycemia and serum creatinine were also determined by enzymatic methods, and urinary albumin excretion in the first morning spot using immunoturbidimetry.

2.3. Definition of risk factors, target organ damage and manifest cardio-renal disease

Hypertension was defined as SBP $\geq$140 mm Hg, diastolic blood pressure DBP $\geq$90 mm Hg, or current use of antihypertensive medication. Diabetes was defined as fasting plasma glucose $\geq$7.0 mmol/l or use of oral antidiabetic drugs and/or insulin. Dyslipidemia was defined as any of the following: total cholesterol $\geq$5 mmol/l, LDL cholesterol $\geq$3 mmol/l, triglycerides $\geq$1.7 mmol/l, HDL-cholesterol $<$1 mmol/l in men and $<$1.2 mmol/l in women or use of lipid-lowering drugs. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m^2. Estimated glomerular filtration rate was determined by the simplified CKD-EPI formula as described by Levey [19]. Microalbuminuria was defined as an albumin/creatinine ratio $\geq$1.9 mg/mmol in men and $\geq$2.8 mg/mmol in women. Resting ECG was acquired by a MAC 5500 device (GE Healthcare, Waukesha, WI, USA) and digitally processed by purpose-written software. ECGs with complete left or right bundle branch block, atrial fibrillation, and paced rhythm or from individuals with a myocardial infarction history were excluded from further analysis. The Sokolow-Lyon index [$SV_1 + RV_{5/6}$] was calculated. A Sokolow-Lyon voltage over 35 mm was considered an ECG sign of left ventricular hypertrophy. The association of arterial stiffness indices with parameters of subclinical organ damage was analyzed only in individuals without a history of cardiovascular events. Coronary artery disease was defined as a history of myocardial infarction or revascularization (coronary artery bypass grafting or percutaneous coronary intervention). We estimated the ten-year risk of fatal cardiovascular disease in individuals between 40 and 65 years of age without manifest cardiovascular disease and diabetes using equation developed by the SCORE project [20] with country-specific coefficients.

2.4. Measurement of large artery properties

Large artery properties were measured using the SphygmoCor device (AtCor Medical Ltd, West Ryde, New South Wales, Australia) in the recumbent position as described previously [21]. Carotid-femoral (cfPWV) and femoral-ankle (faPWV) pulse wave velocity were assessed separately according to recommendations [22]. Consecutive registrations of the pulse waves are ECG-gated and thus the time shift (Δt) between the foot of wave at the first and second sites can be calculated. The distance between the two sites was measured on the body surface. To determine cfPWV, we measured the distance from the jugular fossa to the pulsation of the femoral artery in the groin and subtracted the distance from the jugular fossa to carotid pulsation to obtain the traveled distance (D). The distance between the femoral artery and dorsal pedal/posterior tibial artery was measured to calculate faPWV. PWV was calculated as D (meters)/Δt (seconds). Carotid-ankle PWV (caPWV) was calculated as the sum of carotid-femoral and femoral-ankle traveled distance divided by the sum of carotid-femoral and femoral-ankle time shift. Stiffness index Beta derived from cfPWV and caPWV (cfBETA and caBETA) was calculated by the equation $ln(SBP/DBP) \times 2\varsigma/PP \times PWV^2$, where PWV is cfPWV and caPWV, respectively.

2.5. Statistical analysis

Descriptive statistics is given as mean and standard deviation (SD), or as frequency and percent. The association of scale

parameters in univariate analysis was evaluated using Pearson's or Spearman's correlation, as appropriate. The correlation coefficient (r) with the level of significance is provided in tables. Differences in the strength of association were compared by calculating z statistics for comparison of correlations within a single sample. Data in tables are not adjusted for multiple comparisons. Forward stepwise multiple regression analyses were used to determine parameters independently associated with arterial stiffness indices. Variables associated with arterial stiffness parameters in univariate analysis were included in the multivariate model. Sex was included into all multivariate models. A standardized coefficient beta ($_s\beta$) is reported. A standardized beta of 0.1 indicates that each increase in the independent variable by one SD increases the dependent variable by 0.1 SD. Associations of different arterial stiffness parameters with manifest coronary heart disease (CHD) presence, chronic kidney disease, left ventricular hypertrophy and microalbuminuria were compared by testing the difference in areas under the receiver operating characteristic (ROC) curves using the method described by Hanley and McNeil [23]. Calculations were done using SPSS 19 (IBM Corpora -Somers, NY, USA) and MedCalc 9.2 (MedCalc Software, Mariakerke, Belgium). A two-sided p-value <0.05 was considered statistically significant.

3. Results

In total, data from 809 individuals (mean age 54 ± 13.5 years, 47% of men) were used for this analysis. Population descriptive statistics is provided in Table 1.

3.1. Carotid-femoral vs. carotid-ankle PWV

There was a significant positive correlation between cfPWV and caPWV ($r = 0.77$, $p < 0.0001$). In the univariate analysis, carotid-femoral PWV was more strongly associated with age, cholesterol level, waist circumference, height, and eGFR and less strongly associated with left ventricular hypertrophy, as determined by Sokolow-Lyon criteria, than was carotid-ankle PWV (Table 2). Both cfPWV and caPWV were similarly and positively associated with estimated risk of fatal cardiovascular events determined by SCORE tables. In the stepwise multiple regression analysis (Table 3), determinants of cfPWV were age, mean blood pressure, heart rate, waist circumference, and eGFR, while carotid-ankle PWV was associated with age, mean blood pressure, heart rate, sex, Sokolow-Lyon index, and waist circumference. We did not find any difference in the strength of association with CHD presence between cfPWV and caPWV as assessed by the area under ROC curve (Table 4). On the other hand, carotid-femoral PWV was more closely associated with chronic kidney disease (CKD) presence than carotid-ankle PWV (Table 4).

Table 1
Population descriptive statistics.

Variable	Mean ± SD/n (%)
Age (years)	53.91 ± 13.55
Male sex n (%)	380 (47%)
CHD n (%)	38 (4.7%)
Stroke n (%)	17 (2.1%)
MAU n (%)	23 (2.8%)
LVH n (%)	73 (9%)
CKD n (%)	68 (8.4%)
Hypertension n (%)	370 (46%)
Diabetes n (%)	52 (6.4%)
Obesity n (%)	230 (28.4%)
Systolic BP (mm Hg)	127.34 ± 16.86
Diastolic BP (mm Hg)	69.54 ± 10.92
Body weight (kg)	80.23 ± 16.24
Waist circumference (cm)	93.98 ± 13.63
Hip circumference (cm)	107.77 ± 9.16
Total cholesterol (mmol/l)	5.17 ± 1.01
HDL cholesterol (mmol/l)	1.43 ± 0.42
LDL cholesterol (mmol/l)	2.93 ± 1.29
Glucose level (mmol/l)	5.34 ± 1.12
Albumin/creatinine (mg/mmol)	0.53 ± 4.56
eGFR (ml/min/1.73 m^2)	75.03 ± 12.22
cfPWV (m/s)	8.38 ± 2.32
caPWV (m/s)	9.14 ± 1.6
cfBETA	16.41 ± 9.03
caBETA	18.88 ± 5.86
Sokolow-Lyon index (mm)	22.69 ± 7.59

CHD—coronary heart disease; MAU—microalbuminuria; LVH—left ventricular hypertrophy; CKD—chronic kidney disease; BP—blood pressure; eGFR—estimated glomerular filtration rate; cfPWV—carotid-femoral pulse wave velocity; caPWV—carotid-ankle pulse wave velocity; cfBETA—carotid-femoral stiffness index beta; caBETA—carotid-ankle stiffness index beta.

3.2. Pulse wave velocity vs. stiffness parameter beta

In the univariate analysis, caBETA was less dependent on systolic, diastolic, mean blood pressure and heart rate than caPWV (Table 2). Similarly, cfBETA was less dependent on systolic, diastolic, mean blood pressure and heart rate than cfPWV. In the stepwise multiple regression analysis, beta transformed cfPWV was less dependent on mean blood pressure and heart rate than cfPWV as evident from the explained variance (partial $R^2 = 0.1$ vs. 0.05, Table 2). Similarly beta transformed caPWV was less dependent on mean blood pressure and independent of heart rate as compared to caPWV. When comparing the ROC AUC, cfBETA was more closely associated with CHD presence than cfPWV (0.731 ± 0.03 vs. 0.714 ± 0.04, $p < 0.05$). Similarly, caBETA was more closely associated with CHD presence than caPWV (0.740 ± 0.03 vs. 0.711 ± 0.04, $p < 0.05$).

4. Discussion

Carotid-femoral pulse wave velocity is an established marker of cardiovascular risk. In this study, we performed a comparative analysis of stiffness indices of several segments of the arterial system: carotid-femoral PWV, carotid-ankle PWV, carotid-femoral BETA, and carotid-ankle BETA, in a large random population

Table 2
Correlations between different arterial stiffness parameters and cardiovascular risk factors/parameters of subclinical organ damage.

	cfPWV	caPWV	caBETA	cfBETA	p^1	p^2	p^3
Age (years)	0.66***	0.57***	0.55***	0.66***	***		
Height (cm)	0.11***	–0.03	0.01	–0.09**	*		
Weight (kg)	0.25***	0.21***	0.19***	0.24***			
Waist circumference (cm)	0.41***	0.36***	0.30***	0.35***	*	***	***
Systolic BP (mm Hg)	0.60***	0.57***	0.38***	0.49***		***	***
Diastolic BP (mm Hg)	0.15***	0.15***	–0.044	0.04		***	***
MAP (mm Hg)	0.44***	0.44***	0.189***	0.277***		***	***
Heart rate (/min)	0.16***	0.13***	0.01	0.08*		***	***
Total cholesterol (mmol/l)	0.21***	0.13***	0.11*	0.20**	***		*
LDL cholesterol (mmol/l)	0.15***	0.09*	0.07*	0.14***	**		
Serum glucose (mmol/l)	0.34***	0.30***	0.24***	0.31***			
eGFR (ml/min/1.73 m^2)	0.45***	–0.34***	–0.32***	–0.45***	***		
Albumin/creatinine (mg/mmol)	0.02	0.05	0.05	0.02			
Sokolow-Lyon index (mm)	0.05*	0.17**	0.15**	0.06	***		
SCORE	0.56**	0.55**	0.52**	0.47**		***	***

Correlation coefficients are given, univariate analysis.
p^1 cfPWV vs. caPWV, p^2 cfPWV vs. cfBETA, p^3 caPWV vs. caBETA.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; BP—blood pressure; eGFR—estimated glomerular filtration rate; SCORE—estimated ten-year risk of fatal cardiovascular disease; cfPWV—carotid-femoral PWV; caPWV—carotid-ankle PWV.

Table 3
Determinants of cfPWV, cfBETA, caPWV, caBETA and faPWV in multivariate stepwise regression analysis.

	β	$_s\beta$	R^2	p
cfPWV				
Age (years)	0.070	0.411	0.369	<0.001
Mean blood pressure (mm Hg)	0.051	0.285	0.105	<0.001
Heart rate (/min)	0.036	0.155	0.027	<0.001
Waist circumference (cm)	0.030	0.177	0.022	<0.001
eGFR (ml/min/1.73 m^2)	−0.014	−0.072	0.003	<0.05
$R^2 = 0.524$				
cfBETA				
Age (age)	0.240	0.363	0.296	<0.001
Mean blood pressure (mm Hg)	0.142	0.206	0.054	<0.001
Waist circumference (cm)	0.112	0.168	0.020	<0.001
Heart rate (/min)	0.075	0.083	0.007	<0.001
eGFR (ml/min/1.73 m^2)	−0.062	−0.084	0.004	<0.001
$R^2 = 0.380$				
caPWV				
Age (years)	0.052	0.450	0.330	<0.001
Mean blood pressure (mm Hg)	0.039	0.324	0.142	<0.001
Heart rate (/min)	0.024	0.149	0.016	<0.001
Sex (female)	−0.263	−0.082	0.017	<0.01
Sokolow-Lyon index (mm)	0.020	0.090	0.006	<0.01
Waist circumference (cm)	0.008	0.071	0.009	<0.05
$R^2 = 0.517$				
caBETA				
Age (years)	0.180	0.416	0.282	<0.001
Mean blood pressure (mm Hg)	0.102	0.225	0.061	<0.001
Sex (female)	−1.683	−0.139	0.025	<0.001
Sokolow-Lyon index (mm)	0.053	0.063	0.003	<0.05
$R^2 = 0.371$				

cfPWV—carotid-femoral pulse wave velocity; cfBETA—carotid-femoral stiffness index beta; caPWV—carotid-ankle pulse wave velocity; caBETA—carotid-ankle stiffness index beta; eGFR—estimated glomerular filtration rate; $_s\beta$—standardized coefficient beta.

sample. First, we have demonstrated that addition of femoral-ankle PWV to carotid-femoral PWV has an effect on the strength of association with some cardiovascular risk factors while having no effect on association with coronary heart disease presence. Second, we have shown that beta transformation of PWV may decrease the effect of blood pressure and heart rate on arterial stiffness. Third, we have found that beta transformed PWV is more closely associated with CHD presence that untransformed PWV. Fourth, cfPWV seems to be more closely related to kidney function than caPWV while caPWV may be more closely related to parameters of left ventricular hypertrophy.

We have found a strong positive association ($r = 0.77, p < 0.001$) between cfPWV and caPWV suggesting that caPWV is mostly dependent on central arterial stiffness. This finding is in line with previous studies [10,11] in which baPWV was more dependent on aortic stiffness than on lower extremity arterial stiffness. However, our results also suggest that a large proportion of the total variability of caPWV is explained by cfPWV. This means that caPWV is not solely an index of central arterial stiffness, but a composite index of central and muscular artery stiffness. We have also shown that gender has no independent effect on aortic stiffness while stiffness parameters including lower extremity stiffness such as caPWV and caBETA are increased in men independently of other cardiovascular risk factors. As a new finding, we have shown that addition of femoral-ankle PWV to carotid-femoral PWV decreases the association with age, cholesterol level, and eGFR. This can be explained by only a small effect of these factors on arterial stiffness of muscular arteries [18]. All these findings suggest that caPWV and cfPWV are not interchangeable because muscular arterial stiffness confounds the former, with a measurable effect on the association with certain adverse cardiovascular and renal phenotypes.

rIn our study, cfPWV was more closely associated with renal function than caPWV. To our knowledge, this has not been reported before. In the study by Tanaka [11], cfPWV correlated with eGFR more closely than caPWV ($r = -0.32$ vs. -0.25), but the strength of association was not compared. In our work, the closer association of cfPWV with renal function in univariate analysis was also confirmed by multiple linear regression, in which eGFR was independently associated with cfPWV, but not with caPWV. This means that addition of lower extremity arterial stiffness to aortic stiffness decreases the strength of association with renal function.

On the other hand, caPWV in our study was more strongly associated with left ventricular hypertrophy as determined by the Sokolow-Lyon index. This finding is in line with the study by Yu [24], in which brachial-ankle PWV was more strongly related to left ventricular mass and diastolic function as determined by echocardiography than carotid-femoral PWV. This may be because baPWV and caPWV cover both the central and peripheral arterial territories suggesting that peripheral muscular arteries may contribute to the ventriculo–arterial interaction independently of central arteries. We found a similar strength of association of cfPWV and caPWV with central systolic blood pressure ($r = 0.56$ vs. 0.56, p = n.s.), central pulse pressure (0.58 vs. 0.59, p = n.s.), central augmentation pressure (0.39 vs. 0.38, p = n.s.), and central augmentation index (0.19 vs. 0.23, p = n.s.) estimated using radial applanation tonometry. This suggests that the different strength of association of caPWV and cfPWV with left ventricular hypertrophy is not caused by a stronger association with parameters of central hemodynamics.

There are two possible mechanisms of the PWV increase. The first one is due to structural, and the other one due to functional changes of arterial wall. Structural stiffening of elastic arteries caused by aging and other cardiovascular risk factors is explained by fragmentation and alteration of the elastic fiber network responsible for the buffering function of arteries [8]. Functional stiffening of arteries results from increased blood pressure. Under normal blood pressure, elastic elastin fibers are recruited. Increased blood pressure loads stiffer collagen fibers, thereby increasing arterial stiffness. This explains the nonlinear relationship between blood pressure and PWV [25]. Functional stiffening of arteries can be reversed by blood pressure lowering [26]. In the presence of

Table 4
Comparison of association of different arterial stiffness parameters with cardiovascular events and parameters of subclinical organ damage using the area under receiver operating curve.

	cfPWV	caPWV	caBETA	cfBETA	p^1	p^2	p^3
CHD	0.713 ± 0.04	0.708 ± 0.04	0.742 ± 0.03	0.731 ± 0.03	NS	<0.05	<0.05
CKD	0.731 ± 0.03	0.633 ± 0.03	0.645 ± 0.04	0.741 ± 0.03	<0.001	NS	NS
MAU	0.584 ± 0.06	0.606 ± 0.06	0.584 ± 0.06	0.564 ± 0.06	NS	NS	NS
LVH	0.650 ± 0.03	0.674 ± 0.04	0.662 ± 0.04	0.641 ± 0.03	NS	NS	NS

p^1 cfPWV vs. caPWV, p^2 cfPWV vs. cfBETA, p^3 caPWV vs. caBETA.
CHD—coronary heart disease; CKD—chronic kidney disease; MAU—microalbuminuria; LVH—left ventricular hypertrophy.

structural changes, the stiffening is less dependent on blood pressure [27]. In the study by Guerin, survival of patients with end-stage renal disease was significantly better for subjects whose aortic PWV declined in response to blood pressure lowering compared to individuals without a PWV decrease after blood pressure decrease [28]. In another study, individuals with increased PWV before and after dialysis had increased risk of death compared to subjects with increased PWV before and normal PWV after dialysis [29]. This suggests that the PWV increase due to structural changes is more deleterious than the functional PWV increase caused by increased blood pressure. This led to the development of the blood pressure-independent parameter of arterial stiffness referred to as stiffness parameter Beta [30] or CAVI [31]. In our study, we have shown that Beta transformed PWV is less dependent on blood pressure and heart rate than PWV. This finding is in line with previous reports [14,31]. As a new finding, we have shown that beta transformed PWV is more closely associated with CHD presence than PWV. We speculate this is because stiffness parameter Beta better reflects structural changes of the arterial wall and is less dependent on functional stiffening caused by increased blood pressure, as compared with PWV.

In our study, cfPWV was more strongly related to age, cholesterol level, and eGFR than caPWV while there was no difference in the association with manifest cardiovascular disease. It can be explained by the closer association of caPWV with left ventricular hypertrophy. The similar predictive value of cfPWV and caPWV reported in our study is in line with previously published papers [11,24].

4.1. Study limitations

We have to acknowledge limitations of this work caused by the cross-sectional design of our study and a small number of clinical events in this randomly selected population sample at rather low cardiovascular risk. However, with our sample size, we had a 99% power to detect a 0.05 difference in the area under receiver–operator curve. Thus, the similar association of caPWV and caPWV with CHD cannot be explained by the lack of statistical power. In our study, we determined left ventricular mass by ECG criteria known to have lower sensitivity as compared with echocardiography or magnetic resonance imaging. However, the closer association of caPWV than cfPWV with left ventricular mass as determined by ECG criteria reported in our study is in line with the previously reported closer association of baPWV than cfPWV with left ventricular mass measured using echocardiography [24]. Obesity negatively influences quality of pressure waves recorded, what might influence the strength of association of obesity-related risk factors with PWV.

5. Conclusions

To conclude, our study has shown that all studied parameters of central arterial stiffness are associated with manifest cardiovascular disease, parameters of subclinical organ damage, and cardiovascular risk factors; however, they slightly differ in the strength of association. Addition of lower extremity arterial stiffness to aortic stiffness decreases the strength of association with age, cholesterol level, and glomerular filtration rate while increasing the strength of association with left ventricular hypertrophy determined by the Sokolow-Lyon index and increases gender differences. We have found that beta transformed PWV is less dependent on blood pressure and heart rate and is more closely associated with manifest cardiovascular disease presence than PWV. In the future, prospective studies with hard endpoints such as total and cardiovascular mortality will be needed to confirm our findings.

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Conflicts of interest

None.

Disclosures

None.

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6.4 Vztah mezi vysokým ABI a aortální tuhostí

Snížený poměr kotník-paže (ABI) je diagnostický pro ischemickou chorobu dolních končetin (Ouriel et al., 1982, Fowkes, 1988, Lijmer et al., 1996) a je nezávislým prediktorem kardiovaskulární morbidity a mortality (Heald et al., 2006, Wautrecht et al., 2006). Zatím nebyl jednoznačně prokázán vztah mezi zvýšeným ABI (ABI>1,4) a kardiovaskulárním rizikem. Ve studii MESA byl zvýšený ABI spojen s hypertrofií levé komory nezávisle na subklinické ateroskleróze (Ix et al. rok?). To znamená, že na hypertrofii levé komory u pacientů s inkompresibilitou tepen dolních končetin se podílejí jiné mechanizmy než ateroskleróza. Jedním z těchto mechanizmů může být zvýšená aortální tuhost. Cílem naší studie bylo porovnat aortální rigiditu jako nezávislý marker kardiovaskulárního rizika u pacientů s nízkým (<1,0), normálním (1,0–1,4) a vysokým ABI (>1,4).

Metodika Do studie jsme zařadili 911 pacientů ze studie Czech post-MONICA (náhodně vybraný 1% populační vzorek české populace průměrného věku 54 ± 13,5 let, 47 % mužů). ABI jsme měřili ručním dopplerem, PWV jako parametr aortální tuhosti pomocí přístroje SphygmoCor.

Výsledky Z celkového počtu 911 osob mělo 28 (3,1 %) nízký ABI a 23 (2,5 %) vysoký ABI. Aortální tuhost byla zvýšena u osob s nízkým (11,1 ± 2,8 vs. 8,3 ± 2,3, p <0,001) i vysokým ABI (10,8 ± 2,5 vs. 8,3 ± 2,3, p < 0,001) ve srovnání s jedinci s normálním ABI. Po adjustaci na věk, pohlaví, systolický, diastolický a střední arteriální tlak zůstala aortální tuhost zvýšena u osob s nízkým i vysokým ABI. V logistické regresní analýze byly nezávislými prediktory zvýšeného ABI zvýšená aortální tuhost, glykémie, mužské pohlaví a anamnéza hluboké žilní trombózy.

Diskuse V naší práci jsme jako první prokázali zvýšenou aortální tuhost u osob s vysokým poměrem kotník-paže. To ukazuje na zvýšené kardiovaskulární riziko osob s inkompresibilitou tepen dolních končetin. Zvýšená aortální rigidita může vysvětlit vztah mezi vysokým ABI a hypertrofií levé komory, který není zprostředkován aterosklerózou.

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A high ankle-brachial index is associated with increased aortic pulse wave velocity: the Czech post-MONICA study

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Abstract

Background: Ankle brachial index (ABI) has been increasingly used in general practice to identify individuals with low ABI at high cardiovascular risk. However, there has been no consensus on the clinical significance of high ABI. The aim of our study was to compare aortic stiffness as a marker of cardiovascular risk in individuals with low (<1.0), normal (1.0–1.4), and high ABI (>1.4).

Methods: A total of 911 individuals from the Czech post-MONICA study (a randomly selected 1% representative population sample, aged 54 ± 13.5 years, 47% of men) were examined. ABI was measured using a handheld Doppler and aortic pulse wave velocity (aPWV) using the Sphygmocor device.

Results: Of the 911 individuals, 28 (3.1%) had low ABI and 23 (2.5%) high ABI. There was a U-shaped association between aPWV and ABI. aPWV was significantly higher in individuals with low and high ABI compared with the normal ABI group (11.1 ± 2.8, 8.3 ± 2.3, $p < 0.001$; 10.8 ± 2.5, 8.3 ± 2.3 m/s, $p < 0.001$, respectively). In a model adjusted for age, sex, systolic, diastolic, mean blood pressure and examiner, aPWV remained increased in both extreme ABI groups compared with the normal ABI group. In logistic regression analysis, aPWV together with glucose level, male sex, and a history of deep venous thrombosis were independent predictors of high ABI, while cholesterol was not.

Conclusion: This is the first study showing increased aortic stiffness in individuals with high ABI, presumably responsible for increased left ventricular mass described previously in this group. These findings suggest increased cardiovascular risk of high ABI individuals.

Keywords

Arterial stiffness, high ankle-brachial index, pulse wave velocity

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Introduction

Ankle brachial index (ABI) is the ratio of the higher of ankle pressures to the higher of arm pressures. A low ABI is diagnostic for peripheral arterial disease (PAD) and is associated with increased risk of all-cause mortality, cardiovascular mortality, and total mortality as compared with normal ABI.[1,2]

In contrast with the strong evidence on low ABI, the clinical significance of high ABI (ABI >1.4) is unknown. Most epidemiological studies excluded individuals with high ABI. Few studies comparing cardiovascular risk associated with high ABI have provided discrepant data. Recently, increased left ventricular mass was described in individuals with high ABI.[3] We hypothesized that increased aortic pulse wave velocity

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(aPWV) could be responsible for increased left ventricular mass and increased cardiovascular risk in individuals with high ABI.

The aim of our study was to compare aPWV as an independent predictive factor for all-cause and cardiovascular morbidity and mortality in individuals with low (ABI <1.0), normal (ABI 1.0–1.4), and high ABI (ABI >1.4) in a random population sample.

Methods

Study population

The Czech post-MONICA (MONItoring trends and determinants in CArdiovascular disease) study is a population survey studying trends and determinants of cardiovascular risk factors in a 1% random sample of the Czech population in nine districts of the country. Methods of the Czech post-MONICA study are described elsewhere.[4] Our study includes individuals aged >25 years from the City of Pilsen. The overall response rate in this district was 68.0%. A total of 911 patients had complete data on ABI and aPWV, which represents 98% of patients examined in the district.

Doppler ABI measurement

Appropriately sized cuffs of the mercury sphygmomanometer (Baumanometer; WA Baum, NY, USA) were placed proximal to the ankles and on the right arm. After at least 5 minutes' resting period in the supine position, systolic blood pressure was measured in the right brachial artery, right dorsal pedal, posterior tibial artery, left dorsal pedal, and tibial artery in this order, using a pocket Doppler device with an 8 MHz probe (Dopplex multiTM; Huntleigh, Cardiff, UK). Next, systolic blood pressure was re-measured in the right brachial artery for a second time. If the difference between the first and the second brachial systolic pressure measurements was higher than 10 mmHg, all measurements were repeated. All measurements were performed by two physicians experienced in ABI measurement. ABI was calculated separately for each leg by dividing the higher of the ankle systolic pressures by the brachial systolic pressure. The lower of the two leg ABI values was used in further analysis.

Large artery properties measurement

Measurements were done using a semi-automatic Sphygmocor device (AtCor Medical, Australia) in the recumbent position. The methods of measurement were described in detail in our previous report.[5] aPWV was calculated as the ratio of pulse wave time shift between the carotid and femoral arteries and the distance between the two sides. Consecutive registrations of the pulse waves are electrocardiogram-gated and thus, the time shift between the foot of wave at the first and second sites can be calculated. The distance between the two sites was calculated by subtracting the distance from the jugular fossa to carotid pulsation from the distance from the jugular fossa to the pulsation of the femoral artery in the groin. The average of measurements over a period of 8 s was calculated after the exclusion of extreme values.

Statistical analysis

Descriptive statistics are given as mean and standard deviation or frequency and percentage. Previous studies have demonstrated that subjects with ABI <1.0 and ≥1.4 or with incompressible arteries are at greater risk for cardiovascular disease events and mortality than subjects with normal ABI. Participants were divided into three groups on the basis of ABI according to these cut-points. Characteristics of these groups were compared using the one-way ANOVA test with Turkey's post-hoc test for continuous variables, and the chi-squared test with Bonferroni correction for categorical variables. For continuous variables, when equal variance was violated, the Kruskal–Wallis test was used. The Fisher exact test was employed when the expected number in any cell for a categorical variable was less than 10. Variables significantly differing between the ABI categories were included into binary logistic regression analysis to evaluate factors associated with high ABI. To compare aPWV between the different ABI groups, analysis of variance and a model adjusted for age, sex, systolic, diastolic, mean blood pressure, and observer were used. A two-sided p-value <0.05 was considered to be statistically significant.

Results

Of the 911 individuals with complete data on arterial indices, 28 (3.1%) had low ABI, 860 (94.4%) normal ABI, and 23 (2.5%) high ABI. Of the 23 individuals with high ABI, five had incompressible vessels in one leg and two in both legs. Tables 1 and 2 provide population characteristics by ABI groups.

Compared with individuals with normal ABI, those with low ABI were significantly older, had higher body weight, larger waist and hip circumferences, and higher systolic blood pressure and glucose level. Prevalence of hypertension, diabetes, hyperlipidaemia, and coronary heart disease was higher in these participants compared with the normal ABI group.

Similar to individuals with low ABI, those with high ABI were older, had higher body weight, larger waist

Table 1. Descriptive statistics by ankle brachial index (ABI) groups: continuous variables

Characteristic	Low ABI $n=28$ 3.1%	Normal ABI $n=860$ 94.4%	High ABI $n=23$ 2.5%	Total $n=911$ 100%	p-value for ANOVA	p-value for low vs. normal ABI	p-value for low vs. high ABI	p-value for normal vs. high ABI
Age (years)	63.29 ± 9.24	53.45 ± 13.54	62.74 ± 7.82	53.99 ± 13.49	<0.0001	<0.0001	1.00	<0.01
Total cholesterol (mmol/l)	4.99 ± 1.0	5.17 ± 1.02	5.03 ± 0.99	5.16 ± 1.01	0.528			
Triglycerides (mmol/l)	1.64 ± 0.73	1.5 ± 1.05	1.65 ± 0.83	1.51 ± 1.04	0.606			
HDL-chol (mmol/l)	1.33 ± 0.27	1.43 ± 0.43	1.32 ± 0.29	1.43 ± 0.42	0.085			
LDL-chol (mmol/l)	2.91 ± 0.91	2.92 ± 1.3	2.95 ± 0.79	2.92 ± 1.28	0.993			
Plasma fasting glucose (mmol/l)	6.33 ± 1.99	5.32 ± 1.05	6.74 ± 3.28	5.39 ± 1.23	0.001	<0.01	1.00	<0.05
Height (cm)	167.39 ± 8.17	170.63 ± 9.25	174.04 ± 7.55	170.62 ± 9.21	<0.05	0.14	<0.05	0.13
Weight (kg)	86.57 ± 14.39	80.15 ± 16.49	90.57 ± 10.69	80.61 ± 16.41	<0.01	<0.01	0.97	<0.01
Waist circumference (cm)	104.04 ± 11.36	93.82 ± 13.66	104.35 ± 9.27	94.4 ± 13.7	<0.0001	<0.0001	0.92	<0.001
Hip circumference (cm)	112.46 ± 10.24	107.73 ± 9.37	110.00 ± 5.49	107.93 ± 9.35	<0.05	<0.05	0.314	0.606
Systolic BP (mmHg)	138.85 ± 16.92	127.08 ± 16.95	138.55 ± 17.56	127.7 ± 17.15	0.0001	<0.001	1.00	<0.01
Diastolic BP (mmHg)	67.77 ± 11.94	69.48 ± 10.78	71.77 ± 10.87	69.48 ± 10.81	0.441			
Pulse pressure (mmHg)	71.08 ± 21.76	57.6 ± 19.19	66.77 ± 23.45	58.22 ± 19.53	<0.0001	<0.001	0.723	<0.05
aPWV (m/s)	11.13 ± 2.83	8.3 ± 2.28	10.79 ± 2.5	8.45 ± 2.39	0.0001	<0.0001	0.86	<0.0001

Values are mean ± SD. aPWV, aortic pulse wave velocity; BP, blood pressure; HDL-chol, high-density lipoprotein cholesterol; LDL-chol, low-density lipoprotein cholesterol.

Table 2. Descriptive statistics by ankle brachial index (ABI) groups: categorical variables

Characteristic	Low ABI $n=28$, 3.1%	Normal ABI $n=860$, 94.4%	High ABI $n=23$, 2.5%	p-value for low vs. normal ABI	p-value for low vs. high ABI	p-value for normal vs. high ABI
Male sex	16 (57.1)	393 (45.8)	20 (87)	NS	NS	<0.001
CHD	7 (25)	38 (4.4)	1 (4.3)	<0.001	NS	NS
Stroke or TIA	1 (3.6)	18 (2.1)	1 (4.3)	NS	NS	NS
DVT	2 (7.1)	38 (4.4)	5 (21.7)	NS	NS	<0.05
PE	1 (3.6)	7 (0.8)	2 (8.7)	NS	NS	NS
Smokers	7 (25)	210 (24.6)	1 (4.3)	NS	NS	NS
HT	22 (78.6)	380 (44.5)	16 (69.6)	<0.01	NS	<0.05
DM	11 (39.3)	53 (6.2)	6 (26.1)	<0.001	NS	<0.01
HLP	26 (92.6)	598 (70)	16 (69.6)	<0.05	NS	NS

Values are n (%). CHD, coronary heart disease; DM, diabetes; DVT, deep venous thrombosis; HLP, hyperlipidaemia; HT, hypertension; NS, not significant; PE, pulmonary embolism; TIA, transient ischaemic attack.

circumference, systolic blood pressure and higher glycaemia compared with participants with normal ABI. In the group with high ABI, the male sex was predominant (87% of males). A higher cardiovascular risk profile of individuals with high ABI was suggested by the higher prevalence of hypertension, diabetes, and deep venous thrombosis (DVT) as compared with those with normal ABI.

Compared with the other two groups, individuals with low ABI were more frequently treated with lipid-lowering and antihypertensive drugs (Table 3). On the other hand, the proportion of individuals with high ABI and normal ABI on lipid-lowering drugs did not differ.

aPWV followed a U-shaped curve with regard to ABI (Figure 1). It was significantly higher in participants with low and high ABI compared with the normal ABI group (11.1 ± 2.8 vs. 8.3 ± 2.3 m/s, $p < 0.0001$; 10.8 ± 2.5 vs. 8.3 ± 2.3 m/s, $p < 0.0001$, respectively) and did not differ between individuals with low and high ABI (11.1 ± 2.8 m/s vs. 10.8 ± 2.5 m/s, $p = 0.86$). In a model adjusted for age, sex, systolic, diastolic, mean blood pressure, and examiner, aPWV remained increased in both extreme ABI groups compared with the normal ABI group [9.8 ± 0.3 m/s (95% CI 9.15–10.46) vs. 8.4 ± 0.1 m/s (95% CI 8.25–8.47), $p < 0.001$ for low vs. normal ABI

Table 3. Lipid-lowering and antihypertensive drugs by ankle brachial index (ABI) groups

Type of drug	Low ABI $n=28$ 3.1%	Normal ABI $n=860$ 94.4%	High ABI $n=23$ 2.5%	Total $n=911$ 100%	p-value for low vs. normal ABI	p-value for low vs. high ABI	p-value for normal vs. high ABI
Lipid-lowering drugs	13 (46)	145 (17)	6 (23)	164 (18)	<0.001	NS	NS
Antihypertensive medication	21 (75)	284 (33)	11 (48)	316 (35)	<0.001	NS	NS
ACEIs/ARBs	19 (68)	199 (23)	10 (43)	228 (25)	<0.001	NS	<0.05
Calcium-channel blockers	11 (39)	103 (12)	5 (22)	119 (13)	<0.01	NS	NS
Diuretics	7 (25)	90 (10)	4 (17)	101 (11)	<0.01	NS	NS
Beta-blockers	11 (40)	122 (14)	1 (4)	134 (15)	<0.01	NS	NS
Central antihypertensives	1 (4)	18 (2)	0 (0)	19 (2)	NS	NS	NS
α-blockers	0 (0)	10 (1)	1 (4)	11 (1)	NS	NS	NS

Values are n (%). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

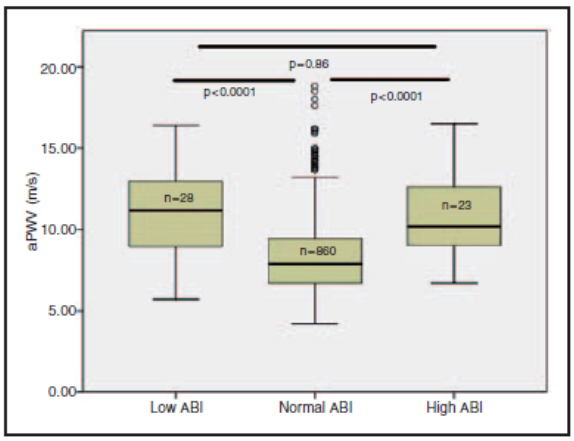

Figure 1. Aortic PWV by ankle brachial index (ABI) subgroups. Patients in the low and high ABI groups had increased aPWV compared with the normal ABI group. aPWV, aortic pulse wave velocity.

group; 9.4±0.4 m/s (95% CI 8.65–10.08) vs. 8.4±0.1 m/s (95% CI 8.25–8.47), $p=0.02$ for high vs. normal ABI group] and no difference was found between low and high ABI groups (9.8±0.3 vs. 9.4±0.4 m/s, $p=0.98$). In the logistic regression analysis, aPWV together with glucose level, male sex, and a history of deep venous thrombosis were independent predictors of high ABI (Table 4).

Discussion

ABI measurement has been increasingly used in general practice to identify individuals with low ABI at high cardiovascular risk. However, because of insufficient evidence, there is no consensus on the clinical significance of high ABI in regard to cardiovascular risk. Most large epidemiological studies have excluded these individuals. There are only a few studies showing inconsistent evidence on cardiovascular risk associated with high ABI. Increased risk of all-cause and cardiovascular mortality in individuals with ABI >1.4 was described in the Strong Heart Study in American Indians[6] and in the Cardiovascular Health Study.[7] Similarly, increased risk of cardiovascular mortality at ABI levels below 1.1 and above 1.3 was noted among Japanese haemodialysis patients.[8] Contrary to these findings, the cardiovascular event rates in the Atherosclerosis Risk in Community (ARIC) study did not differ between individuals with high and normal ABI over a mean follow-up period of 12 years.[9] There is also disagreement on the cardiovascular risk profile associated with high ABI. While the prevalence of diabetes was increased in the high ABI group in some studies,[6,7,10,11] there was no difference in others.[10,12] This discrepancy among studies could be explained by the different methods of ABI measurement used. While studies measuring ABI by Doppler showed increased risk associated with high ABI (Strong Heart Study and Cardiovascular Health Study), others measuring ABI by the oscillometric method (ARIC study)[13] did not find increased risk associated with high ABI. As we and others have shown,[12] the difference between Doppler and oscillometric ABI increases with increasing ABI. Thus oscillometric devices underestimate high ABI. Moreover, an oscillometric device is not able to identify incompressible arteries. Thirty percent of individuals with high ABI had incompressible leg arteries in our study.

Table 4. Parameters associated with high ankle brachial index in logistic regression analysis

	B	OR (95% CI)	SE	Wald	*p*-value
Plasma fasting glucose (mmol/l)	0.33	1.39 (1.05–1.86)	0.14	5.45	0.02
aPWV (m/s)	0.31	1.36 (1.16–1.64)	0.09	12.29	0.001
Sex (male)	−2.02	7.52 (1.76–36.9)	0.77	6.87	0.009
DVT	1.97	7.2 (2.3–22.4)	0.58	7.6	0.022
Age (years)	0.55	1.73 (0.78–3.82)	0.41	1.82	0.18
Weight (kg)	0.32	1.38 (0.48–3.98)	0.54	0.35	0.55
Waist circumference (cm)	−0.07	0.94 (0.29–3.02)	0.6	0.01	0.91
Systolic BP (mmHg)	0.04	1.18 (0.79–1.76)	0.2	0.68	0.41

$r^2 = 0.2$, $p < 0.001$. aPWV, aortic pulse wave velocity; DVT, history of deep venous thrombosis; SE, standard error.

An ABI <0.9 is considered to be a sign of lower extremity PAD. There is increasing evidence showing that ABI values previously considered low normal are associated with a poor outcome similar to patients with ABI <0.9. In the Multi Ethnic Study of Atherosclerosis, individuals with ABI 0.9–1.10 had higher levels of subclinical atherosclerosis in the carotid and coronary arteries than those with ABI 1.10–1.30.[14] Similarly, in the Strong Heart Study, total and cardiovascular mortality risk increased at ABI <1.10. These findings and increased aPWV in individuals with ABI 0.9–1.0 compared with ABI 1.0–1.4 (10.52 ± 2.9 m/s vs. 8.24 ± 2.14 m/s, $p < 0.0001$) made us choose ABI = 1.0 as the cut-off for the low ABI group.

We used ABI >1.4 as the cut-off value for the high ABI group. There were 59 individuals with an ABI between 1.3 and 1.4. When setting the cut-off value for high ABI to 1.3, the difference in aPWV between the low and high ABI groups became significant (11.1 ± 2.8 m/s vs. 9.2 ± 2.5 m/s, $p < 0.001$), while the difference between the normal and high ABI groups remained significant (8.3 ± 2.3 m/s vs. 9.2 ± 2.5 m/s, $p < 0.01$). After adjustment for age, sex, systolic, diastolic, mean blood pressure, and examiner, the difference between normal and high ABI was no longer significant [8.4 ± 0.2 m/s (95% CI 8.0–8.8) vs. 8.6 ± 0.3 m/s (95% CI 8–9.1)]. This means that in individuals with ABI between 1.3 and 1.4, aPWV is not significantly increased.

The observed prevalence of high ABI in our population sample was 2.5%. It is higher than the 1.15% and 1.2% prevalence of ABI >1.4 in the Cardiovascular Health Study and ARIC study, respectively, but lower than the 9.2% prevalence reported in the Strong Heart Study. An even higher prevalence was reported in individuals with chronic renal failure (23.7%) or on dialysis (41.7%).[15] The prevalence of high ABI observed in our random population sample of the Czech population was comparable with that of low ABI. This suggests that high ABI is not a rare condition in the population.

An abnormally increased ABI is widely believed to be associated with medial arterial calcification caused by calcification of the arterial media and the internal elastic membrane of muscular arteries.[16] Vascular calcification is the consequence of dysregulation between promotion and inhibition of calcification often seen in chronic kidney disease, diabetes mellitus, atherosclerosis and aging.[17] Thus a high ABI is not exclusively associated with diabetes as commonly believed. The prevalence of diabetes in the high ABI group in our study (25%) is similar to the 28% prevalence in the Multi-Ethnic Study of Atherosclerosis and the 25% prevalence in the Cardiovascular Health Study. The lower prevalence of diabetes in our and other studies may be due to the definition of diabetes based on use of antidiabetic drugs and fasting glucose level. Definitions based also on the oral glucose tolerance test or glycated haemoglobin level may have resulted in an increased prevalence of diabetes in the high ABI group.

Another important finding is that cholesterol level is not associated with high ABI. The prevalence of hyperlipidaemia was increased in the low ABI group compared with the normal ABI group, and no difference was found between the normal and high ABI groups. There was no difference in cholesterol levels between the groups, which was most likely due to the high rates of use of lipid-lowering drugs in low ABI individuals (Table 3). This might be yet another proof of the concept that high ABI is linked to stiffness and not to atherosclerosis.

Increased aortic stiffness increases systolic and pulse pressure while decreasing diastolic blood pressure. In our and other studies,[3,7] high ABI individuals had slightly increased systolic and pulse pressure, while no difference was seen in diastolic blood pressure compared with the normal ABI group. This could be caused by the frequent use of antihypertensive therapy in the high and low ABI groups in our study.

The increased aortic stiffness persisting elevated after blood pressure control is a sign of intrinsic vasculopathy as noted by Guerin et al.[18] This suggests that the increased aortic stiffness in high ABI is due to structural changes of the aorta, presumably calcifications, seen in the muscular arteries of these individuals.

Lately, there has been increasing evidence on the association between atherosclerosis and DVT.[19] Conventional cardiovascular risk factors have been shown to increase the risk of DVT. The proposed mechanism behind this association is arterial and venous endothelial dysfunction. In our study, we have shown increased prevalence of DVT in the high ABI group compared with the normal ABI group. The higher prevalence of hypertension, diabetes and obesity in these individuals can cause endothelial dysfunction leading to higher risk of DVT. The non-significant difference between the low and normal ABI groups is probably caused by lack of power to detect this difference due to the small sample size. Another explanation for the increased rates of DVT in high ABI individuals may be increased lower extremity arterial stiffness due to medial arterial calcification. Increased lower extremity arterial stiffness has been shown to decrease arterial flow volume in the lower extremities of diabetic patients.[20] A decreased flow volume in the arterial system presumably leads to blood stasis in the venous system, an abnormality of Virchow's triad associated with thrombus formation.

To the best of our knowledge, this is the first study showing increased aPWV in individuals with ABI >1.4. Increased arterial stiffness in patients with PAD has been reported previously. In the Health ABC study, the prevalence of ABI <0.9 increased with increasing quartiles of aPWV.[21] In the Rotterdam study, the presence of PAD was associated with a significantly increased aPWV.[22] Matsumae reported higher aPWV in non-diabetic haemodialysis patients with PAD compared with non-diabetic haemodialysis individuals without PAD.[23] In our study, we found a U-shaped association between ABI and aPWV. In agreement with other studies, we observed increased aPWV in PAD individuals. Moreover, we observed increased aPWV in the high ABI group which was comparable with those with low ABI. Increased aPWV has been shown to be an independent predictive factor for all-cause and cardiovascular mortality, cardiovascular disease, fatal and non-fatal coronary events and fatal strokes in patients with various levels of cardiovascular risk.[24] Increased aortic stiffness through increased left ventricular afterload leads to left ventricular hypertrophy. Increased aPWV can explain the atherosclerosis-independent increase in left ventricular mass recently described in high ABI individuals in Multi-Ethnic Study of Atherosclerosis.

To summarize, we have shown increased aortic pulse wave velocity in individuals with high ABI. The increased aPWV in these individuals indicates increased cardiovascular risk. Prospective studies using the Doppler method of ABI measurement are needed to confirm the increased cardiovascular risk associated with high ABI.

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Conflict of interest

None

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6.5 Vztah mezi centrálním a brachiálním krevním tlakem a hypertrofií levé komory

Hypertrofie levé komory je projevem subklinického orgánového poškození (Mancia et al., 2013) a je spojena se zvýšeným rizikem kardiovaskulární morbidity a mortality (Levy et al., 1990, Levy et al., 1994). Arteriální hypertenze je nejčastější příčinou hypertrofie levé komory v obecné populaci (Ganau et al., 1990). Zatímco střední arteriální tlak je konstantní ve velkých tepnách, systolický a pulzní tlak se zvyšují směrem od srdce do periférie. Tento fenomén zvaný amplifikace systolického a pulzního tlaku je způsoben odrazem tlakové vlny v periférii a závisí na viskoelastických vlastnostech cévní stěny. Ve studiích byl centrální tlak v aortě lepším prediktorem kardiovaskulárních příhod než brachiální krevní tlak (Wang et al., 2009, Vlachopoulos et al., 2010). Centrální tlak vykazuje i lepší asociaci s hypertrofií levé komory detekované pomocí ultrazvuku než brachiální krevní tlak. Cílem naší práce bylo porovnat sílu asociace mezi centrálním a brachiálním tlakem s hypertrofií levé komory detekované pomocí EKG kritérií.

Metodika Pro analýzu jsme použili data 728 pacientů ze studie Czech post-MONICA. Centrální krevní tlak v aortě jsme stanovili pomocí aplanační tonometrie z radiální pulzové vlny pomocí validované transformační funkce přístroje SphygmoCor. EKG známky hypertrofie LK byly diagnostikovány pomocí Sokolow-Lyonova indexu a Cornellova produktu.

Výsledky Z 657 pacientů zařazených do analýzy mělo 17 (9,4 %) osob mladších 45 let a 43 (9 %) osob starších 45 let hypertrofii levé komory. V mnohočetné lineární regresní analýze byl Sokolow-Lyonův index u mladších jedinců asociován pouze s mužským pohlavím a nízkým BMI, přičemž žádnou nezávislou asociaci s krevním tlakem jsme nenalezli. U starších osob byla hypertrofie levé komory ve vztahu s vyšším centrálním i brachiálním tlakem. V samostatných binárních logistických regresních analýzách adjustovaných na klinické proměnné byl centrální tlak více asociován s hypertrofií levé komory než brachiální krevní tlak.

Diskuse Neinvazivně stanovený centrální tlak u osob nad 45 let je v těsnějším vztahu s EKG známkami hypertrofie levé komory než brachiální tlak. To podporuje hypotézu užšího vztahu centrálního tlaku se subklinickým orgánovým poškozením. EKG kritéria hypertrofie levé komory u mladších pacientů nejsou asociovány s krevním tlakem, což

naznačuje nízkou senzitivitu EKG pro detekci hypertrofie LK v této skupině. Toto zjištění je v souladu s výsledky jiných studií, které ukázaly, že EKG známky hypertrofie LK u mladších osob nejsou podmíněny hypertrofií LK (Larsen et al., 2002, Sohaib et al., 2009).

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ORIGINAL ARTICLE

Relation of central and brachial blood pressure to left ventricular hypertrophy. The Czech Post-MONICA Study

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Central blood pressure (BP) has been shown to be a better predictor of target organ damage and cardiovascular events than brachial BP. Whether central BP is a better predictor of left ventricular hypertrophy (LVH) determined by electrocardiography (ECG) is not known. Radial applanation tonometry and ECG were performed in 728 subjects from the Czech Post-MONICA Study (a randomly selected 1% population sample). LVH was determined using the Sokolow–Lyon index and Cornell product; central pressure was derived from radial pulse. Of 657 subjects included in the analysis, 17 (9.4%) below 45 years and 43 (9%) over 45 years had LVH. In multiple linear regression analysis, the Sokolow–Lyon index in younger individuals was only associated with male sex and low BMI, with no association with BP found. In older individuals, LVH was associated with higher central and brachial BP. In separate binary logistic regression analyses adjusted for covariates, the odds ratio for central systolic pressure was higher than those for brachial systolic and pulse pressure in LVH prediction. Noninvasively determined central pressure in subjects over 45 years is more strongly related to ECG LVH than brachial pressure. This further supports a closer association of central pressure with target organ damage. Voltage criteria of LVH are not independently associated with central or brachial BP in younger individuals.
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Keywords: left ventricular hypertrophy; central blood pressure; electrocardiography; Cornell product; Sokolow–Lyon index; population random sample

Introduction

Left ventricular hypertrophy (LVH) is a sign of subclinical organ damage associated with increased cardiovascular morbidity and mortality.[1–3] LVH is characterized by an abnormal increase in left ventricular myocardial mass due to increased afterload (arterial hypertension, aortic stenosis) or diastolic overload (aortic or mitral regurgitation, dilated cardiomyopathy), which can be detected by electrocardiography (ECG), echocardiography or magnetic resonance imaging. ECG is the least expensive and most widely used method of LVH diagnosis in clinical practice. Many different ECG criteria of LVH have been proposed over the years. A common feature of all ECG criteria is their high specificity but low sensitivity compared with echocardiographic LVH diagnosis.[4] The most commonly used ECG criteria for LVH proposed by the European Society of Hypertension are the Cornell voltage product and the Sokolow–Lyon index.[5]

Arterial hypertension is the main cause of LVH in the general population.[6] The prevalence of LVH is heavily dependent on the population studied, and on the LVH diagnostic procedure and criteria used. The prevalence of LVH determined by echocardiography in hypertensive patients has been estimated at 25% and 26% in males and females, respectively. In the normotensive population, the LVH prevalence is 14% and 20%, respectively.[7] The prevalence of ECG LVH in the general population ranges from 2.7–5.4%.[8,9]

Although mean blood pressure (BP) is constant in the conduit arteries, the systolic and pulse pressures vary from central to peripheral arteries due to wave

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reflections and viscoelastic properties of the arterial wall. Central BP indices have been shown to be better predictors of cardiovascular events compared with brachial BP.[10,11] Similarly, central BP has been shown to be more closely related to left ventricular mass, as detected by echocardiography,[12] and carotid artery hypertrophy[13] than brachial BP. Whether central BP is more closely related to the ECG LVH criteria than brachial BP has not been studied. The present study was aimed at investigating the impact of central and brachial BP on LVH assessed by ECG criteria.

Methods

Study population
The Czech Post-MONICA (MONItoring trends and determinants in CArdiovascular disease) Study is a population survey studying trends and determinants of cardiovascular risk factors in a random sample of the Czech population in nine districts of the country. The selection of subjects was made from the registry of the General Health Insurance company keeping, by law, a list of all those insured. Health insurance is mandatory for all Czech citizens. Methods of the Czech Post-MONICA Study have been published elsewhere.[14] Our study included individuals aged over 25 years who were examined between 2008 and 2009 in Pilsen (Plzeň) City district. The overall response rate in this district was 68.0%. A total of 728 patients underwent ECG and radial applanation tonometry on the day of the study visit.

BP was measured in triplicate in the right arm with the subject in the sitting position after at least 5 min at rest. Standard mercury sphygmomanometers and correctly sized cuffs were used. The participant's right arm was supported at heart level. The maximum inflation level was determined before the actual measurement. BP values were recorded to the nearest 2 mm Hg. The mean value of the last two readings was used for further analysis. Hypertension was defined as systolic BP $\geqslant$140 mm Hg, diastolic BP $\geqslant$90 mm Hg or current use of antihypertensive medication. Diabetes was defined as fasting plasma glucose $\geqslant$7.0 mmol l^{-1} or use of oral antidiabetic drugs and/or insulin. Dyslipidemia was defined as total cholesterol $\geqslant$5 mmol l^{-1} or high-density lipoprotein-cholesterol $<$1 mmol l^{-1} in men and $<$1.2 mmol l^{-1} in women or use of lipid-lowering drugs.

Applanation tonometry
Central pressure blood indices were measured using a semi-automatic Sphygmocor device (AtCor Medical Ltd, West Ryde, Australia) in the recumbent position after 5 min at rest. The methods of measurement were described in detail in our previous reports.[15,16] Briefly, radial artery pressure waveform was recorded at the right radial artery. The corresponding central aortic pressure waveform was derived using validated generalized transfer function. Calibration was done using brachial systolic and diastolic BP obtained immediately before the test using an oscillometric device (Omron M5, Omron, Kyoto, Japan). Central systolic, diastolic and mean BPs were estimated using the validated technique of pulse wave analysis.

Electrocardiography
Resting ECG was acquired by a MAC 5500 device (GE Healthcare, Waukesha, WI, USA) and digitally processed by purpose-written software. ECGs with complete left or right bundle branch block, atrial fibrillation, paced rhythm and from individuals with coronary event history were excluded from further analysis. The Cornell voltage product ($R_{aVL} + S_{V3}$(+6 in women) $\times$ QRS duration) and Sokolow–Lyon index ($S_{V1} + R_{V5/6}$) were calculated. A Cornell voltage product over 2440 mm $\times$ ms and Sokolow–Lyon voltage over 35 mm were considered ECG signs of LVH.

Statistical analysis
Descriptive statistics is given as mean and standard deviation, or as frequency and percent. As previous studies reported that ECG signs of LVH in younger individuals were not associated with increased cardiovascular risk,[17] separate analyses were performed for individuals below and over 45 years. Characteristics of groups with and without LVH were compared using the 2-tailed *t*-test for independent samples for continuous variables, and by the χ^2 test for categorical variables. Fisher's exact test was used instead of the χ^2 test, if the expected number in any cell for categorical variable was $<$10. Because of significant co-linearity of individual BP modalities, separate multiple linear regression models were composed to assess the association between the Sokolow–Lyon index and BP in individuals below 45 years of age. Except for central and brachial BP, variables significantly associated with the Sokolow–Lyon index in univariate analyses were entered into these models. A standardized coefficient beta (β_s) is reported. A standardized beta of 0.1 indicates that when the independent variable increases by one standard deviation, the dependent variable increases by 0.1 standard deviation. In individuals over 45 years separate binary logistic regression analyses adjusted for age, sex, body height, BMI, heart rate and the use (type) of antihypertensive medication were performed to compare central and brachial BP in ECG-based LVH prediction (fulfilling Sokolow–Lyon voltage criteria or Cornell product criteria). The predictive power of central and brachial BP was also compared by testing the difference between areas under receiver operating characteristic curves using the method described by Hanley and McNeil.[18] Calculations were done using SPSS 17 (IBM Corpora-

tion, Somers, NY, USA) and MedCalc 9.2 (MedCalc Software, Mariakerke, Belgium). A two-sided *P*-value <0.05 was considered statistically significant.

Results

A total of 728 participants who underwent applanation tonometry and ECG were enrolled in the study. In all, 71 individuals with complete left ($n=5$) or right ($n=8$) bundle branch block, atrial fibrillation ($n=9$), paced rhythm ($n=6$) or history of coronary artery disease ($n=43$) were excluded from further analysis. In the age group below 45 years, there were 17 subjects (9.4%) with ECG LVH, of these, 16 with Sokolow–Lyon voltage criteria and 1 with Cornell voltage product criteria (Table 1). In separate linear regression analyses, the Sokolow–Lyon index was only associated with male sex and low BMI, while no association with central or brachial BP was observed (Table 2).

There were 43 individuals (9%) over the age of 45 years with ECG signs of LVH; of these, 22 (4.6%) fulfilled Sokolow–Lyon voltage criteria, 25 (5.3%) Cornell product criteria and 4 (1%) had both voltage criteria for LVH. Most of the participants over 45 years with ECG signs of LVH had hypertension. Individuals with the Cornell voltage product LVH criterion had higher BMI compared with individuals without this criterion (30.9 ± 4.6 vs $28.5\pm5.2\,kg\,m^{-2}$, $P<0.05$), while Sokolow–Lyon index was associated with lower BMI (26.6 ± 3.4 vs $28.7\pm5.2\,kg\,m^{-2}$, $P<0.05$). Both brachial and central BP indices were higher in the LVH group (Table 3).

Relationship of central and brachial BP to ECG LVH

As ECG LVH (Cornell product or Sokolow–Lyon voltage criteria) was associated with BP only in individuals over 45 years, further analyses were performed only in this group. In separate binary logistic regression analyses adjusted for age, sex, heart rate and the use (type) of antihypertensive medication, the odds ratios (OR) for central systolic (OR: 1.11; 95% CI: 1.08–1.15) and pulse pressure (OR: 1.10; 95% CI: 1.07–1.14) were higher than those for brachial systolic (OR: 1.05; 95% CI: 1.03–1.07) and pulse pressure (OR: 1.034; 95% CI: 1.02–1.060) in LVH prediction (Table 4). Models including central BP indices were able to explain the higher proportion of variability as assessed by Nagelkerke R^2 (0.46 and 0.36 vs 0.20 and 0.18 for central systolic and pulse pressure vs brachial systolic and pulse pressure, respectively).

A stronger association of central BP with ECG LVH was also confirmed in the receiver operating characteristic analysis (Figure 1). In this analysis, central systolic BP was a better predictor of LVH diagnosed by the Sokolow–Lyon criteria or Cornell voltage product than brachial systolic BP (area under the curve (AUC) of 0.90 ± 0.02 vs 0.83 ± 0.03, $P<0.05$) and brachial pulse pressure (AUC of 0.90 ± 0.02 vs 0.81 ± 0.03, $P<0.05$). The difference between central pulse pressure and brachial pulse pressure (AUC of 0.87 ± 0.03 vs 0.81 ± 0.03, $P>0.05$), and brachial systolic BP (AUC of 0.87 ± 0.03 vs 0.83 ± 0.03, $P>0.05$) was not significant. Similarly, we did not find any difference between central systolic and pulse pressure (AUC of 0.9 ± 0.02 vs 0.87 ± 0.03, $P>0.05$).

Table 1 Comparison of characteristics of patients below 45 years of age with and without electrocardiographic left ventricular hypertrophy

	LVH (n = 17)	*Without LVH (n = 164)*	P
Age (years)	34.6 ± 5.9	35.2 ± 5.3	NS
Sex (male), *n* (%)	15 (88.2)	69 (42.1)	<0.001
BMI ($kg\,m^{-2}$)	24.0 ± 2.8	25.6 ± 4.8	<0.05
Weight (kg)	78.1 ± 12.2	77.4 ± 17.1	NS
Hypertension, *n* (%)	1 (5.9)	14 (8.5)	NS
Diabetes, *n* (%)	1 (5.9)	3 (1.8)	NS
Brachial SBP (mm Hg)	121.5 ± 7.7	116.1 ± 11.1	NS
Brachial DBP (mm Hg)	68.5 ± 9.1	69.3 ± 12.4	NS
Brachial PP (mm Hg)	53.6 ± 10	46.8 ± 15	NS
Central SBP (mm Hg)	113.4 ± 11.4	108.5 ± 13.8	NS
Central DBP (mm Hg)	76.5 ± 8.9	76.4 ± 9.5	NS
Central PP (mm Hg)	36.92 ± 6.4	34.1 ± 7.9	NS
aPWV ($m\,s^{-1}$)	5.65 ± 0.99	5.99 ± 1.15	NS

Abbreviations: aPWV, aortic pulse wave velocity; BMI, body mass index; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; NS, not significant; PP, pulse pressure; SBP, systolic blood pressure.

Discussion

In previous studies,[10–12] central BP was shown to be more closely associated with LVH determined by echocardiography. In the present study, we extended

Table 2 Separate multiple linear regression analyses comparing association of sex, BMI, central and brachial blood pressure with the Sokolow–Lyon index in individuals below 45 years of age

Variable	β_s	P
Model 1 $R^2=0.24$		
Central SBP (mm Hg)	0.10	0.15
Sex (female)	−0.47	<0.001
BMI ($kg\,m^{-2}$)	−0.15	<0.05
Model 2 $R^2=0.22$		
Central PP (mm Hg)	0.09	0.20
Sex (female)	−0.48	<0.001
BMI ($kg\,m^{-2}$)	−0.14	<0.05
Model 3 $R^2=0.23$		
Brachial SBP (mm Hg)	0.04	0.56
Sex (female)	−0.48	<0.001
BMI ($kg\,m^{-2}$)	−0.14	<0.05
Model 4 $R^2=0.24$		
Brachial PP (mm Hg)	0.09	0.23
Sex (female)	−0.47	<0.001
BMI ($kg\,m^{-2}$)	−0.15	<0.05

Abbreviations: BMI, body mass index; βs, standardized β; PP, pulse pressure; SBP, systolic blood pressure.

Table 3 Comparison of characteristics of patients over 45 years of age with and without electrocardiographic left ventricular hypertrophy

	LVH (n = 43)	*Without LVH (n = 433)*	*P*
Age (years)	64.0 ± 6.5	61.0 ± 7.9	<0.01
Sex (male) *n* (%)	25 (58.1)	200 (46.2)	NS
BMI (kg m^{-2})	29.3 ± 4.4	28.7 ± 5.2	NS
Weight (kg)	82.9 ± 14.5	82.0 ± 16.8	NS
Height (m)	167.7 ± 8.4	168.1 ± 9.4	NS
Hypertension, *n* (%)	39 (90.7)	242 (55.9)	<0.001
ACEI or ARB, *n* (%)	21 (43.9)	123 (28.4)	<0.01
Calcium blockers, *n* (%)	12 (27.9)	72 (16.6)	0.056
Diuretics, *n* (%)	13 (30.2)	58 (13.4)	<0.01
Beta blockers, *n* (%)	12 (27.9)	66 (15.2)	<0.05
Diabetes, *n* (%)	5 (11.6)	45 (10.4)	NS
Stroke, *n* (%)	1 (2.3)	9 (2.1)	NS
Brachial SBP (mm Hg)	151.5 ± 18.3	130.8 ± 16.0	<0.001
Brachial DBP (mm Hg)	67.5 ± 9.8	70.4 ± 10.9	<0.05
Brachial PP (mm Hg)	84.2 ± 20.2	60.4 ± 18.7	<0.001
Central SBP (mm Hg)	149.8 ± 19.8	128.0 ± 17.1	<0.001
Central DBP (mm Hg)	84.58 ± 11.8	80.9 ± 9.4	<0.05
Central PP (mm Hg)	64.1 ± 18.5	47.1 ± 13.9	<0.001
Heart rate (bpm)	63.8 ± 10.2	67.8 ± 11.3	<0.05
aPWV (m s^{-1})	9.71 ± 1.90	8.63 ± 2.29	<0.01

Abbreviations: aPWV, aortic pulse wave velocity; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; PP, pulse pressure; SBP, systolic blood pressure.

Table 4 Association of blood pressure indices with left ventricular hypertrophy in separate binary logistic regression analysis adjusted for age, sex, heart rate and the use (type) of antihypertensive medication in individuals over 45 years of age

	OR	*95% CI*	*Nagelkerke R²*	P
cSBP (mm Hg)	1.113	1.076–1.152	0.46	<0.001
cPP (mm Hg)	1.101	1.065–1.139	0.36	<0.001
bSBP (mm Hg)	1.046	1.025–1.068	0.20	<0.001
bPP (mm Hg)	1.034	1.018–1.058	0.18	<0.001

Abbreviations: bPP, brachial pulse pressure; bSBP, brachial systolic blood pressure; CI, confidence interval; cPP, central pulse pressure; cSBP, central systolic blood pressure; OR, odds ratios.

this finding to LVH determined by ECG. We found that central systolic pressure is more closely related to LVH detected by the Sokolow–Lyon index or Cornell product than brachial systolic and pulse pressure. A closer association of central pressure with left ventricular mass was also found in the population-based Strong Heart Study[12] in which central systolic BP was more strongly associated with LVH determined by echocardiography than central pulse pressure, brachial systolic and pulse pressure. On the other hand, central pulse pressure was more strongly related to vascular hypertrophy and the extent of atherosclerosis than brachial BP in this study.[13] Similarly, in a Taiwanese cohort,[10] central systolic BP was the best correlate for left

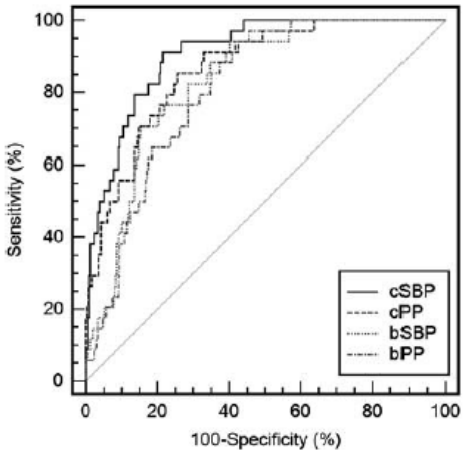

Figure 1 Receiver operating characteristic curves comparing age, sex, heart rate and the use (type) of antihypertensive medication adjusted central and brachial BP in LVH predication in individuals over 45 years of age.

ventricular mass and an independent predictor of cardiovascular mortality, whereas both central systolic and pulse pressures were the best correlates for intima-media thickness and estimated glomerular filtration rate.

Both systolic and pulse pressures are mainly determined by arterial compliance, whereas systolic pressure is also determined by total peripheral resistance. Recently, reduction of reflection magnitude that is mainly determined by total peripheral resistance was shown to be an independent predictor of left ventricular mass reduction induced by antihypertensive medication.[19] The association of systolic BP with total peripheral resistance can explain its closer association with LVH than pulse pressure.

In our study, we did not find any difference in BP and the prevalence of arterial hypertension in young participants below 45 years of age with or without LVH. With the current sample size, we had a 94% power to detect the systolic BP difference of 10 mm Hg in individuals <45 years. We also did not find any difference in another parameter of subclinical organ damage—aortic pulse wave velocity—between individuals with and without LVH in the age group below 45 years, whereas there was a significant difference in subjects over 45 years. Most of the individuals with LVH in this younger age group were men fulfilling almost exclusively the Sokolow–Lyon voltage criteria for LVH. In multiple linear regression with the current sample size ($n = 181$), we had a 98% power to detect a medium size effect of BP on the Sokolow–Lyon index, but we found only the male sex and low BMI to be associated with this index. These results suggest that increased ECG voltage in young subjects is not necessarily a sign of increased left ventricular mass.

Several other factors like the heart proximity to the chest wall, conduction properties of the tissue above the heart, location of the heart within the thorax, and intraventricular and transmural pressures determine the voltage amplitude.[20] The positive predictive value of ECG LVH in this age group is also decreased by the low prevalence of LVH in young individuals. Our findings are in agreement with the results of the Copenhagen Heart Study[21] in which young subjects with voltage criteria of LVH had the same cardiovascular risk as those with normal ECG. Recently, no association between Cornell product and left ventricular mass determined by magnetic resonance was found in healthy young men, while there was only a weak association between the Sokolow–Lyon index and left ventricular mass.[17] On the other hand, in older subjects, a modest association between ECG parameters of LVH and left ventricular mass detected by echocardiography was found.[22,23] This indicates that the amplitude criteria of LVH have little practical use in detecting LVH in young subjects. Neither from previous studies nor from ours is it clear at what age ECG signs of LVH start to be associated with BP and LVH determined by echocardiography or magnetic resonance. In our study, moving the cut off age to 50 years had no effect on results (there were 50 subjects aged 46–50 years, but none had ECG LVH). Future studies should address this issue.

A limitation of the present study is that the effect of pressure overload on LVH was assessed using episodic BP measured at rest. Owing to the 24 h BP variability, this may not fully represent the pressure load on the left ventricle during the whole day. This can explain the observed weak-to-moderate association between central BP and LVH. Furthermore, in individuals with arterial hypertension, we did not account for arterial hypertension duration. Antihypertensive medication may have weakened the association between BP and LVH. Also antihypertensive medication may have different effects on central and brachial BP. All these factors significantly affect LVH development and magnitude. However, all these factors had a similar effect on central and brachial BP, and thus should not significantly influence the observed closer association of central BP with LVH.

In conclusion, our study has shown for the first time a closer association of central systolic BP with electrocardiographic signs of LVH in individuals over 45 years of age compared with brachial BP. This study provides another piece of information about the association between hemodynamic and target organ damage. We did not find a significant difference in BP and arterial hypertension prevalence in individuals with or without electrocardiographic LVH and aged <45 years, suggesting that there are other factors considerably influencing ECG voltage in this age group.

What is known about this topic

- Central blood pressure is a better predictor of target organ damage and cardiovascular events than brachial blood pressure.
- Central BP is a better predictor of left ventricular hypertrophy determined by echocardiography than brachial blood pressure.

What this study adds

- Noninvasively determined central pressure in subjects over 45 years is more strongly related to ECG LVH than brachial pressure.
- Voltage criteria of left ventricular hypertrophy are not independently associated with central or brachial BP in younger individuals.

Conflict of interest

The authors declare no conflict of interest.

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6. Diskuse

Výsledky předkládané disertační práce jsou *in extenso* diskutovány v přiložených a recenzovaných článcích; zde uvádím jejich souhrn.

V prvním tematickém okruhu této práce jsme se věnovali srovnání běžně používané dopplerovské metody stanovení poměru kotník-paže s novou metodou měření ABI založenou na oscilometrickém měření. Výhodou nové metody je, že vyžaduje minimální zkušenosti vyšetřujícího a provádí současně měření na všech 4 končetinách, což snižuje variabilitu měřeného krevního tlaku. Zjistili jsme však, že hodnoty ABI stanovené pomocí srovnávaných metod se významně liší. Proto hodnotu ABI stanovenou pomocí automatického oscilometrického zařízení BOSO ABI nelze zaměňovat se standardním dopplerovým měřením poměru kotník-paže. Rozdíl mezi dopplerovskou a oscilometrickou metodou měření ABI se zvyšuje s rostoucí hodnotou ABI, proto oscilometrická metoda není vhodná pro diagnostiku pacientů s inkompresibilitou tepen dolních končetin. Proto jsme v dalších pracích zabývajících se inkompresibilitou tepen dolních končetin používali dopplerovskou metodu měření ABI. Nicméně vysoká negativní prediktivní hodnota umožňuje použití oscilometrického přístroje BOSO ABI jako screeningového nástroje pro ischemickou chorobu dolních končetin, kde jedním z hlavních cílů je vyloučit onemocnění. Minimální dovednosti a malá časová náročnost předurčuji oscilometrickou metodu měření ABI pro screening v klinické praxi.

Zjištěný rozdíl mezi dopplerovým a oscilometrickým měření ABI lze částečně vysvětlit oscilometrickou metodou měření krevního tlaku. Oscilometricky stanovený systolický krevní tlak se vypočítává na základě hodnoty středního arteriálního tlaku stanoveného z oscilací tepny, které jsou závislé na různých faktorech, z nichž nejdůležitější je arteriální tuhost (van Popele et al., 2000). Proto úroveň tuhosti kotníkových tepen může ovlivnit tlak měřený oscilometrickou metodou.

V literatuře existují nekonzistentní údaje o shodě mezi dopplerovým a oscilometrickým způsobem měření ABI. Některé studie v souladu s našimi výsledky nenašly shodu mezi metodami (Ramanathan et al., 2003, Nukumizu et al., 2007, Aboyans et al., 2008), zatímco jiné popsaly dobrou shodu (Cortez-Cooper et al., 2003, Beckman et al., 2006). Jiné studie používaly nevhodné statistické metody, jako je korelační analýza

(Adiseshiah et al., 1987, Mundt et al., 1992, MacDonald et al., 2008). V souladu s většinou studii jsme ale zjistili vysokou negativní prediktivní hodnotu oscilometrické metody pro stanovení nízkého ABI (Beckman et al., 2006, Mehlsen et al., 2008).

V další části jsme se věnovali srovnání vlivu kardiovaskulárních rizikových faktorů na tuhost aorty a tepen dolních končetin. V naší práci jsme ukázali, že věk a kardiovaskulární rizikové faktory jako hypertenze, diabetes, dyslipidemie a chronické onemocnění ledvin mají významný vliv na aortální tuhost, přičemž pouze věk a hypertenze mají významný vliv na tuhost tepen dolních končetin. Rozdílný vliv věku a kardiovaskulárních rizikových faktoru na sledované tepny lze vysvětlit rozdíly v jejich histologické stavbě. Zatímco sledované faktory vedou ke fragmentaci elastických lamel v tepnách elastického typu, v muskulárních tepnách dolních končetin způsobují hlavně změny hladkosvalových buněk a kolagenu. Dále jsme zjistili, že zvýšený kotníkový systolický tlak není asociován pouze se zvýšenou tuhostí tepen dolních končetin, ale i se zvýšenou tuhostí aorty, a to nezávisle na ostatních kardiovaskulárních rizikových faktorech včetně brachiálního tlaku. Přitom hodnota systolického tlaku na noze byla více závislá na aortální tuhosti než na tuhosti tepen dolních končetin. Zvýšený přenos pulzatilní energie ze srdce do periférie, jako projev porušené nárazníkové funkce aorty a ztráty rozdílu impedancí mezi aortou a muskulárními tepnami, může vysvětlit pozorovaný vztah mezi tuhostí aorty a hodnotou kotníkového systolického tlaku. Za normálních okolností rozdíl v impedancích mezi aortou a muskulárními tepnami způsobuje odraz tlakových vln, což chrání mikrocirkulaci před pulzatilním poškozením. Naše výsledky naznačují, že zvýšený kotníkový systolický tlak může být parametrem zvýšeného přenosu pulzatilní energie do periférie. To může vysvětlit nezávislou prediktivní hodnotu kotníkového systolického tlaku v predikci kardiovaskulárního rizika popsanou v některých studiích (Hietanen et al., 2008, Hietanen et al., 2011).

Dále jsme v naši práci ukázali, že u osob se sníženým poměrem kotník-paže je tuhost tepen dolních končetin falešně podhodnocena. Tento fenomén lze vysvětlit poklesem tlaku za významnou stenózou, což snižuje tuhost tepen dolních končetin, která je kromě jiného závislá na krevním tlaku. Jiným zdůvodněním může být změna morfologie tlakové vlny za stenózou s posunutím začátku tlakové vlny, která byla v literatuře u pacientů s ICHDK popsána (Kempczinski, 1982). Přitom začátek tlakové vlny se používá ke stanovení arteriální tuhosti. Dalším vysvětlením poklesu tuhosti tepen dolních končetin u pacientů s ICHDK může být prodloužení vzdálenosti, kterou

projde tlaková vlna vlivem kolaterální cirkulace. Z výsledku naší práce vyplývá, že metody stanovující tuhost aorty spolu s tuhostí tepen dolních končetin (např. brachiálně-kotníková PWV nebo CAVI) by se u pacientů s ICHDK neměly používat, protože jejich hodnota může byt falešně podhodnocena.

Vzhledem k našemu zjištění, že vliv kardiovaskulárních rizikových faktorů na mechanické vlastnosti aorty a tepen dolních končetin se liší, věnovali jsme se v dalším tematickém okruhu vlivu přidání tuhosti tepen dolních končetin k tuhosti aorty na asociaci s kardiovaskulárními rizikovými faktory a subklinickým orgánovým poškozením. V práci jsme ukázali, že přidání tuhosti tepen dolních končetin k aortální tuhosti snižuje sílu asociace s věkem, hladinou lipidů a hodnotou glomerulární filtrace. Toto zjištění lze vysvětlit menším vlivem uvedených kardiovaskulárních rizikových faktorů na tuhost muskulárních tepen než na tuhost elastických tepen. Na druhou stranu, přidání tuhosti tepen dolních končetin k aortální tuhosti zvýšilo sílu asociace s hypertrofií levé komory diagnostikované pomocí EKG kritérií. Z výsledků této studie vyplývá, že metody stanovení arteriální tuhosti kombinující tuhost aorty s tuhostí muskulárních tepen nelze zaměňovat za metody stanovující tuhost centrálních elastických tepen. Na druhou stranu jsme mezi metodami nezjistili rozdíl ve vztahu k manifestnímu kardiovaskulárnímu onemocnění. Toto zjištění je v souladu s nedávno publikovanou prací (Tanaka et al., 2009), ve které baPWV měla srovnatelnou schopnost predikovat kardiovaskulární riziko jako cfPWV. Bližší asociace caPWV s hypertrofií levé komory zjištěná v naší studii naznačuje, že kromě tuhosti aorty ovlivňuje hypertrofii LK i tuhost tepen dolních končetin. To potvrzuje i jiná studie (Yu et al., 2008), ve které baPWV vykazovala větší míru asociace s diastolickou funkcí a hypertrofií levé komory (diagnostikované pomocí echokardiografie) než cfPWV.

V naší studii jsme dále ukázali, že BETA transformace PWV snižuje závislost PWV na krevním tlaku a srdeční frekvenci. Proto lze předpokládat, že parametr tuhosti BETA je víc závislý na strukturálních změnách cévní stěny zvyšujících cévní tuhost, přičemž PWV je závislá jak na strukturálních změnách cévní stěny, tak i na zvýšené tuhosti vlivem zvýšeného tlaku. Zjištění, že BETA má lepší schopnost predikovat manifestní kardiovaskulární onemocnění než PWV naznačuje, že zvýšení arteriální tuhosti vlivem strukturálních změn cévní stěny je závažnější než zvýšení cévní tuhosti způsobené zvýšeným krevním tlakem. To vysvětluje, proč ve studii pacientů s terminální ledvinovým onemocněním (Guerin et al., 2001) měly osoby reagující na

pokles tlaku poklesem PWV nižší riziko mortality ve srovnání s jedinci, u kterých se PWV po poklesu tlaku nesnížila. Naše výsledky naznačují, že parametr tuhosti BETA může být lepším prediktorem kardiovaskulárního rizika než běžně používaná rychlost pulzové vlny, protože poukazuje na strukturální změny cévní stěny. V budoucnu budou potřebné studie srovnávající použití parametru tuhosti BETA jako terapeutickéhocíle a standardních terapeutických cílů.

Dále jsme v naší práci jako první prokázali zvýšenou aortální tuhost u osob s vysokým poměrem kotník-paže (inkompresibilitou tepen dolních končetin). To znamená, že inkompresibilita tepen dolních končetin je markerem zvýšené arteriální tuhosti i v jiných arteriálních oblastech. Zvýšená tuhost aorty může vysvětlit zvýšenou hmotnost levé komory, která byla popsána u osob s vysokým ABI (Wattanakit et al., 2007). Zvýšená aortální tuhost, zvýšením centrálního systolického a pulzního tlaku, vede ke zvýšení afterloadu (dotížení) levé komory. To způsobuje hypertrofii LK a zvyšuje požadavky srdce na dodávku kyslíku. V naši práci měly osoby se zvýšeným ABI vyšší výskyt hypertenze, diabetu, obezity a anamnézy hluboké žilní trombózy ve srovnání se skupinou s normálním ABI. Vyšší výskyt diabetu v této skupině je ve shodě s jinými studiemi (Resnick et al., 2004, O'Hare et al., 2006, Aboyans et al., 2008, Allison et al., 2008). Vyšší výskyt hluboké žilní trombózy u pacientů s vysokým ABI zatím nebyl v literatuře popsán. Domníváme se, že mechanizmus spojující zvýšenou arteriální tuhost a hlubokou žilní insuficienci je endoteliální dysfunkce, která se uplatňuje v patogeneze obou onemocnění (Gresele et al., 2010, van Bussel et al., 2011). Horší kardiovaskulární rizikový profil u pacientů s vysokým ABI v naší studii je ve shodě s jinými studiemi, které popsaly zvýšené kardiovaskulární riziko osob s inkompresibilitou tepen dolních končetin (Resnick et al., 2004, O'Hare et al., 2006). Proto nejenom nízký ABI, ale i vysoký ABI se musí považovat za znak vysokého kardiovaskulárního rizika.

V poslední části naší práce jsme se zabývali srovnáním síly asociace mezi centrálním a brachiálním tlakem s hypertrofií levé komory detekované pomocí EKG kritérií. Zjistili jsme, že neinvazivně stanovený centrální tlak u osob nad 45 let je v těsnějším vztahu s EKG známkami hypertrofie levé komory než brachiální tlak. Naše zjištění je v souladu s jinými pracemi, které stanovovaly známky hypertrofie levé komory pomocí echokardiografických parametrů (Wang et al., 2009, Roman et al., 2010). Bližší vztah centrálního systolického tlaku (jehož hodnota je ovlivněna tuhostí a

průměrem hrudní aorty i tepovým objemem) s hypertrofií levé komory lze vysvětlit tím, že centrální tlak představuje skutečnou tlakovou zátěž levé komory. Na druhou stranu je hodnota brachiálního systolického a pulzního tlaku kromě faktorů ovlivňujících centrální tlak ovlivněna i takzvaným fenoménem amplifikace systolického a pulzního tlaku, který zvyšuje hodnotu brachiálního tlaku nad úroveň centrálního tlaku. Naše zjištění podporuje hypotézu užšího vztahu centrálního tlaku se subklinickým orgánovým poškozením.

V naší práci nebyla EKG kritéria hypertrofie levé komory u mladších pacientů asociována s krevním tlakem, což naznačuje nízkou senzitivitu EKG pro detekci hypertrofie LK v této skupině. Toto zjištění je v souladu s výsledky jiných studií, které ukázaly, že EKG známky hypertrofie LK u mladších osob nejsou podmíněny hypertrofií LK (Larsen et al., 2002, Sohaib et al., 2009). Nízkou senzitivitu EKG kritérií hypertrofie LK lze vysvětlit tím, že kromě hypertrofie levé LK i množství jiných faktorů ovlivňuje amplitudu vln na EKG. Mezi nejvýznamnější faktory patří vzdálenost srdce od hrudní stěny, vodivé vlastnosti tkáně nad srdcem a hodnota intraventrikulárního a transmurálního tlaku v srdci (Feldman et al., 1985). Senzitivita EKG kritérií hypertrofie LK je u mladých osob dále snížená nízkou prevalencí osob s hypertrofií LK v této skupině. Naše a jiné práce ukazují, že EKG kritéria hypertrofie LK založené na amplitudě vln mají malou schopnost detekovat přítomnost hypertrofie LK u mladších osob.

7. Závěry

1. Výsledky oscilometrické a dopplerovské metody měření poměru kotník-paže nelze zaměňovat. Oscilometrická metoda systematicky nadhodnocuje nízké hodnoty ABI a podhodnocuje vysoké hodnoty ABI. Přesto ji lze její pro vysokou negativní prediktivní hodnotu použít pro screening ischemické choroby dolních končetin.
2. Věk a kardiovaskulární rizikové faktory mají na tuhost tepen dolních končetin menší vliv než na tuhost aorty. Zvýšený poměř kotník-paže jako projev inkompresibility tepen dolních končetin není asociován pouze se zvýšenou tuhostí tepen dolní končetiny, ale i se zvýšenou tuhostí aorty. Osoby s ischemickou chorobou dolních končetin mají falešně sníženou tuhost tepen dolních končetin měřenou jako rychlost šíření pulzové vlny mezi femorální tepnou a kotníkovými tepnami.
3. Přidání tuhosti tepen dolních končetin k aortální tuhosti ovlivňuje sílu asociace s některými kardiovaskulárními rizikovými faktory, nemá však vliv na asociaci s manifestním kardiovaskulárním onemocněním. Beta transformace PWV snižuje závislost PWV na krevním tlaku a může zlepšit prediktivní sílu tohoto parametru.
4. Zvýšená tuhost aorty u osob s inkompresibilitou tepen dolních končetin prostřednictvím zvýšení impedance aorty zvyšuje systolický tlak v aortě, což vede ke zvýšení afterloadu levé komory a její hypertrofii.
5. Neinvazivně stanovený centrální krevní tlak v aortě je u osob nad 45 let lepším prediktorem hypertrofie levé komory detekované pomocí EKG kritérií než brachiální krevní tlak. EKG kritéria hypertrofie levé komory u osob pod 45 let nejsou asociovaná s brachiálním nebo centrální tlakem. To potvrzuje výsledky jiných studií, že EKG známky hypertrofie LK u mladších osob nejsou hypertrofií LK podmíněné.

8. Conclusions

1. The results of oscillometric and Doppler methods of ankle-brachial index measurement cannot be interchangeably used in diagnosing peripheral arterial disease. The oscillometric method systematically overestimates low ABI values and underestimates high ABI values. However, its high negative predictive value allows using it as a screening tool for peripheral arterial disease.
2. The effect of cardiovascular risk factors on arterial stiffness differed between arterial territories. Age and cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, and chronic kidney disease affect aortic stiffness, while only age and hypertension have a significant effect on lower extremity stiffness. Increased ankle-brachial index is not only associated with increased lower extremity arterial stiffness, but also with increased aortic stiffness. Lower extremity arterial stiffness is spuriously decreased in individuals with lower extremity peripheral arterial disease.
3. Addition of femoral-ankle PWV to carotid-femoral PWV has an effect on the strength of association with some cardiovascular risk factors while having no effect in predicting the presence of coronary heart disease. Beta transformation of PWV decreases the effect of blood pressure and heart rate on arterial stiffness. Furthermore, beta transformed PWV is a better predictor of coronary heart disease presence that untransformed PWV. Carotid-femoral PWV seems to be more closely related to kidney function than caPWV while caPWV may be more closely related to parameters of left ventricular hypertrophy.
4. Increased aortic stiffness in patients with lower extremity arteries incompressibility increases aortic blood pressure through increased aortic impedance, which may lead to left ventricular hypertrophy.
5. Non-invasively measured central systolic blood pressure in individuals over 45 years of age is more closely associated with electrocardiographic signs of left ventricular hypertrophy as compared to brachial blood pressure. We did not find a significant difference in blood pressure and arterial hypertension prevalence in individuals with or without electrocardiographic LVH less than 45 years of age, suggesting that there are other factors considerably influencing ECG voltage in this age group.

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