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## Arterial Stiffness and Hypertension: Chicken or Egg?

**Gary F. Mitchell, MD**

Cardiovascular Engineering, Inc., Norwood, MA

### Introduction

Hypertension is highly prevalent in the US and worldwide. In the US, one in three adults (~73 million people) has hypertension. The financial and human costs of hypertension are substantial. The estimated costs attributable to hypertension in the US alone in 2010 were \$70 billion direct costs for medical treatments and \$24 billion indirect costs due to lost productivity.<sup>1</sup> Awareness and treatment of hypertension have improved considerably over the past several decades: >80% of all people with hypertension are aware of the condition and 75% are using antihypertensive medications.<sup>2,3</sup> However, despite enormous effort and treatment-related expenditures, only 53% of those with documented hypertension have their blood pressure controlled.<sup>3</sup> Older age (Figure 1), left ventricular hypertrophy and obesity are important risk factors for uncontrolled or drug resistant hypertension.<sup>4</sup> Importantly, the foregoing are also risk factors for increased aortic stiffness.<sup>5</sup>

Over the past 2 decades, measures of aortic stiffness have emerged as important risk factors for progression of blood pressure and incident cardiovascular disease (CVD). Carotid femoral pulse wave velocity (CFPWV), a measure of aortic wall stiffness, increases markedly with age, particularly after midlife. For example, Framingham Heart Study (FHS) investigators have shown that the prevalence of carotid-femoral pulse wave velocity (CFPWV) greater than 12 m/s increases from a few percent prior to age 50 years to over 60% after 70 years of age (Figure 2A). Importantly, elevated CFPWV is associated with high risk for incident hypertension (Figure 2B) and CVD (Figure 2C). Figure 2C should be interpreted within the context that a normal value (<95<sup>th</sup> percentile) for CFPWV in a healthy FHS reference sample <50 years of age was 8.1 m/s.<sup>6</sup>

Pulse pressure (PP), which is simply systolic minus diastolic pressure from a conventional blood pressure recording, is another measure of aortic stiffness that is widely available but generally ignored when stratifying risk and formulating a treatment plan. PP is sensitive to stiffness of the aortic wall and the balance between aortic flow and diameter in the proximal aorta.<sup>6</sup> PP is also affected by wave reflection and the ventricular interaction with a given reflected wave.<sup>7,8</sup> Elevated PP increases systolic pressure and contributes heavily to

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Gary F. Mitchell, MD, Cardiovascular Engineering, Inc., 1 Edgewater Drive, Suite 201A, Norwood, MA 02062, Phone: (781) 255-6930, Fax: (781) 255-6931, GaryFMitchell@mindspring.com.

#### Disclosures

Dr. Mitchell is owner of Cardiovascular Engineering, Inc., a company that develops and manufactures devices to measure vascular stiffness and serves as a consultant to and receives honoraria from Novartis and Merck. The content of this brief review was presented during the Ninth International Workshop on Structure and Function of the Vascular System, Paris, France, February 6–8, 2014.

development of predominant or isolated systolic hypertension, i.e., wide PP hypertension. Thus, aortic stiffness, as indicated by elevated PP, might be viewed as an inevitable accompaniment of isolated systolic hypertension. However, age relations between PP, which is derived from blood pressure, and CFPWV, the current reference standard for aortic wall stiffness, are complex and potentially divergent, leading to ambiguity and disagreement regarding the role that arterial stiffness plays as precursor versus complication of hypertension.

### Arterial stiffness and blood pressure progression: chicken or egg?

A common interpretation of known relations between arterial stiffness and hypertension is that elevated blood pressure, particularly PP, increases pulsatile aortic wall stress, which accelerates elastin degradation.<sup>9–13</sup> Thus, hypertension is viewed as an accelerated form of vascular aging that leads to aortic stiffening. However, several studies have shown that higher levels of carotid or aortic stiffness in normotensive individuals are associated with accelerated blood pressure progression and increased risk for incident hypertension during follow-up.<sup>14–18</sup> Relations between stiffness measures and future blood pressure generally persisted in models that adjusted for initial values of blood pressure and other known or suspected risk factors for hypertension. In addition, age relations of PP and CFPWV may not be consistent with the premise that high blood pressure and excessive pressure pulsatility contribute to aortic stiffening. In the FHS cohort, aortic wall stiffness, as indicated by CFPWV, increases monotonically from early adulthood (Figure 3). The increase in CFPWV in early adulthood may be attributable in part to a concurrent increase in diastolic and mean arterial pressure prior to midlife,<sup>19</sup> consistent with the potential for a bidirectional relation between hypertension and arterial stiffness in younger adults.<sup>20</sup> In contrast, PP, which is the pulsatile component of blood pressure that drives repetitive strain and contributes to fragmentation of aortic elastin, falls from early adulthood into midlife and then rises dramatically thereafter. The basis for the fall in PP from early adulthood into midlife, followed by a nonlinear transition into rapidly increasing PP, remains speculative and represents an important deficit in our current understanding and opportunity for further investigation of the pathogenesis of systolic hypertension. Nevertheless, this pattern of age relations suggests that in a community-based sample, aortic wall stiffening precedes and contributes to the substantial late life increase in PP that is associated with high incidence of predominantly systolic hypertension in older people.

One of the foregoing studies of relations between arterial stiffness and incident hypertension also examined, in the same (FHS) cohort, relations between initial blood pressure and progression of arterial stiffness as assessed by CFPWV.<sup>15</sup> The authors found that the initial value of CFPWV was strongly associated with subsequent stiffness progression. However, after accounting for the initial value of CFPWV, no blood pressure component (systolic, diastolic or mean) entered the model for future stiffness.<sup>15</sup> These results provide support for the hypothesis that aortic stiffness may antedate and contribute to the development of hypertension.

Several recent longitudinal studies evaluated the correlates of progressive aortic stiffening and found mixed results with respect to relations between initial blood pressure and

progressive aortic stiffening.<sup>15;21–25</sup> Wildman et al evaluated change in CFPWV during 2 years of follow-up in a relatively small (N=152) and young (20–40 years old) biracial cohort and found accelerated stiffening in African Americans and in association with baseline or change in various measures of adiposity.<sup>22</sup> Baseline and change in blood pressures components were not, however, related to stiffness progression. Benetos et al examined a cohort of persistently normotensive and persistently treated hypertensive volunteers followed for 6 years and found that baseline age, heart rate and presence of treated hypertension were associated with CFPWV progression in a multivariable model, whereas baseline levels of SBP and DBP were not related to CFPWV progression.<sup>21</sup> In contrast, Birru et al,<sup>25</sup> El Koudary et al<sup>23</sup> and AlGhatrif et al<sup>24</sup> found relations between baseline SBP and progression of PWV in multivariable models, although El Koudary et al appear to have not included a term for baseline CFPWV in their model. The foregoing mixed results regarding relations between baseline blood pressure and accelerated progression of arterial stiffness suggests that the relation appears to be sufficiently modest that it is difficult to detect consistently.

A number of basic and clinical studies have demonstrated that insults that increase aortic stiffness directly, generally by disrupting elastin in the aortic wall, are associated with subsequent development of hypertension. Studies performed in mouse models of impaired elastin expression have shown that aortic stiffness is increased and diameter is reduced early, before the increase in systolic pressure and that subsequent increments in systolic pressure are inversely proportional to elastin content in the aorta.<sup>26</sup> Similarly, children with Williams syndrome (elastin haploinsufficiency) have increased arterial stiffness at a relatively young age, well before development of hypertension.<sup>27</sup> Increasing elastin expression through introduction of an ectopic copy of the human elastin gene can rescue the arterial phenotype in elastin deficient mice.<sup>28</sup> Administration of a high dose combination of vitamin D3 and nicotine or a combination of warfarin and vitamin K produces aortic medial elastocalcinosis, stiffening of the aorta, increased PWV and PP, and isolated systolic hypertension with no antecedent increase in mean arterial pressure.<sup>29;30</sup> Recently, alterations in diet alone were shown to increase aortic PWV early (1 mo) after introduction of a high fat, high sucrose (HFHS) diet, before an increase in systolic blood pressure, which occurred at 6 mo.<sup>31</sup> HFHS diet was associated with activation of inflammatory pathways and oxidant stress in the aortic wall, resulting in reduced bioavailability of nitric oxide. Activity of the NO-sensitive enzyme transglutaminase-2 was increased, resulting in increased crosslinking of matrix proteins in the aortic media, which increases aortic wall stiffness. Thus, the HFHS model recapitulates the temporal sequence of early aortic stiffening followed by subsequent development of hypertension and provides a readily accessible model of hypertension induced by a primary increase in aortic stiffness.

## Clinical relevance of the role of aortic stiffness in the pathogenesis of hypertension

Mechanisms leading from aortic wall stiffening to systolic hypertension remain incompletely elucidated. Ultimately, hypertension will be present if aortic stiffening and PP widening result in elevation of systolic blood pressure to a level that meets the diagnostic

threshold for hypertension. However, as shown in Figure 3, stiffening (pulse wave velocity) is not necessarily associated with PP widening. Aortic geometry and flow may mediate the varying relations between wall stiffness and pressure pulsatility. Aortic lumen area increases markedly in late childhood and adolescence in order to accommodate increasing flow associated with somatic growth. The aorta continues to enlarge throughout life, particularly in midlife, possibly in response to midlife weight gain. In contrast, elastic fiber production ceases in childhood. Aortic remodeling is therefore associated with thinning and increased stress and strain on elastin, which stiffens the aortic wall because a greater fraction of load bearing is transferred to much stiffer collagen fibers. Because aortic characteristic impedance to pulsatile flow (a major determinant of forward wave amplitude and PP) is more sensitive to diameter than wall stiffness, remodeling to a larger diameter may reduce pressure pulsatility even as it exacerbates wall stiffness and pulse wave velocity. In midlife, aortic remodeling may approach a limit wherein further increments in lumen diameter are either attenuated or are offset by (nonlinear) increments in wall stiffness as thinning of elastic fibers transfers a growing percentage of load onto collagen. PP will then begin to rise in proportion to the ongoing increase in pulse wave velocity (Figure 3). This relatively simple paradigm may explain the ability of pulse wave velocity in middle-aged and older adults to predict subsequent blood pressure progression and incident hypertension<sup>15</sup> as well as major CVD events.<sup>32</sup>

While there may be disagreement regarding the role that stiffness plays in the pathogenesis of hypertension, there is consensus that blood pressure is difficult to control in patients with hypertension and increased arterial stiffness.<sup>4,33</sup> When cases of uncontrolled hypertension are categorized by blood pressure pattern, the majority of cases have increased systolic pressure as the reason for failure to control their blood pressure (Figure 4). After midlife in particular, when the prevalence of hypertension is high, the overwhelming majority of uncontrolled cases had residual isolated systolic hypertension (black bars, Figure 4).<sup>34</sup> This observation implies that failure to control blood pressure is predominantly a problem of failure to control elevated PP.

The contribution of arterial stiffness to the pathogenesis of hypertension and drug resistance has potentially important clinical implications. All drugs currently approved and used for treatment of hypertension were designed to reduce the steady flow component of blood pressure, i.e., diastolic and mean arterial pressure, either by reducing peripheral vascular resistance or cardiac output. Some drugs, such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and low dose diuretics have coincidental favorable effects on arterial stiffness,<sup>35–40</sup> and there is post-hoc evidence that better matching between hemodynamic abnormality and treatment selection may improve outcomes.<sup>41</sup> However, drugs that have a predominant or exclusive effect on mean arterial pressure may be suboptimal for treatment of an individual with predominant or exclusive elevation of systolic pressure due to increased aortic stiffness and wide PP. In such cases, mean arterial pressure may be normal or minimally elevated whereas systolic pressure may be 20 to 60 mm Hg or more above the target pressure for blood pressure control. Reducing systolic pressure by reducing mean arterial pressure with vasodilators may be suboptimal in such patients because diastolic and mean arterial pressure may be reduced to potentially hazardous levels. In addition, an increase in stroke volume or cardiac output following

administration of a vasodilator may fail to reduce<sup>42</sup> or may even increase PP,<sup>43</sup> potentially worsening the hemodynamic component of blood pressure that gave rise to hypertension.

Dissociation between pathogenesis of hypertension and approaches to treatment likely contributes to the predominance of isolated systolic hypertension among hypertensive patients who fail to reach blood pressure goal during treatment (Figure 4) and to the marked reduction with advancing age in the proportion of patients who achieve target blood pressure (Figure 1).<sup>34;44</sup> The proportions of hypertension subtypes in recent surveys underscore the importance of aortic stiffness as a contributor to the pathogenesis of hypertension. The prevalence of isolated diastolic hypertension, which represents an isolated elevation of mean arterial pressure with a low-to-normal PP, is low in the United States, even in young adults.<sup>45</sup> The predominance of isolated systolic hypertension underscores an urgent need to shift the focus from resistance vessel structure and function to large artery structure and function. The triple threat combination of a high prevalence of predominantly systolic hypertension in older people, resistance of wide PP systolic hypertension to currently available drug therapy and aging of the world population provides an urgent mandate to clarify the role that stiffness plays in the pathogenesis of hypertension.

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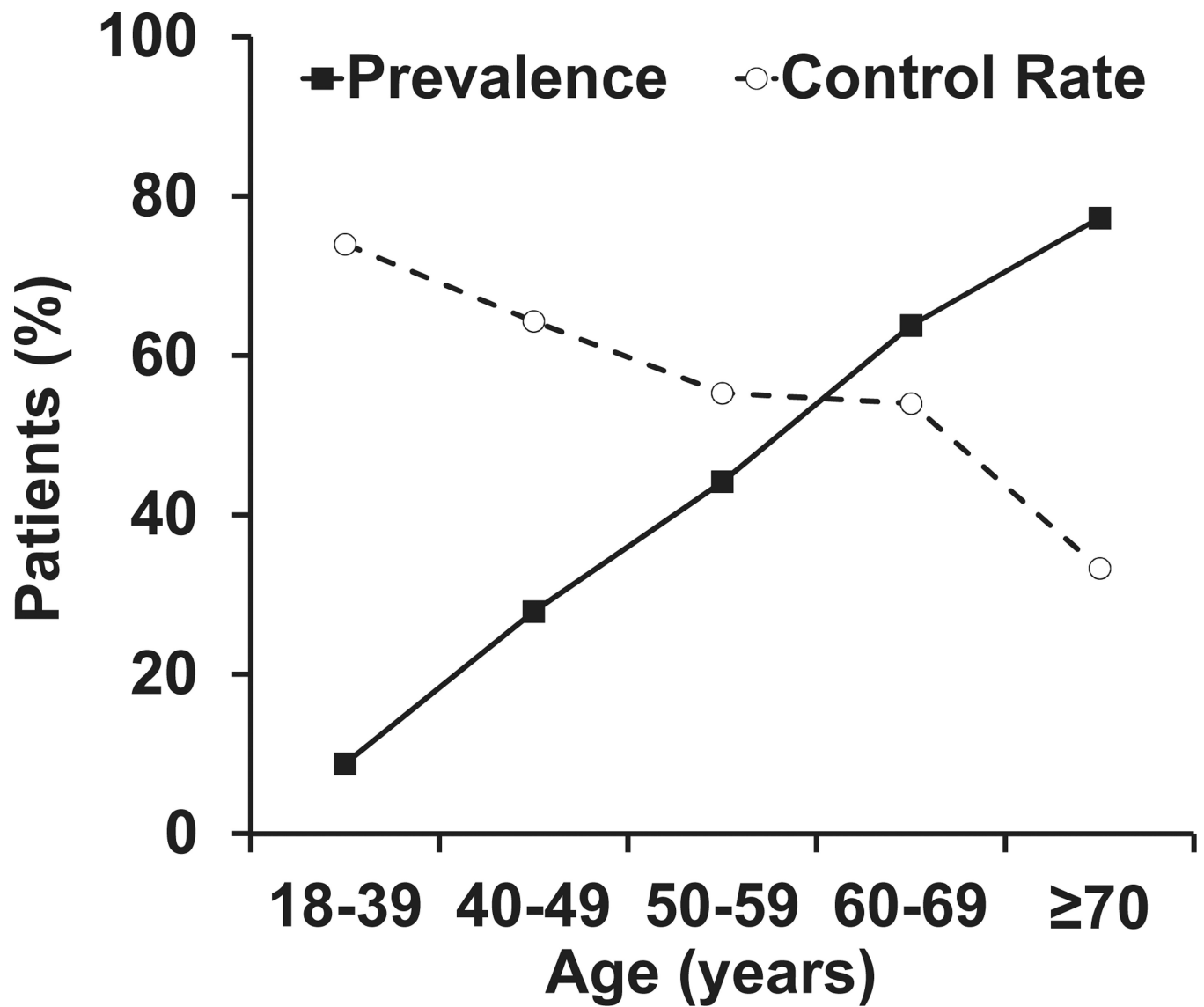
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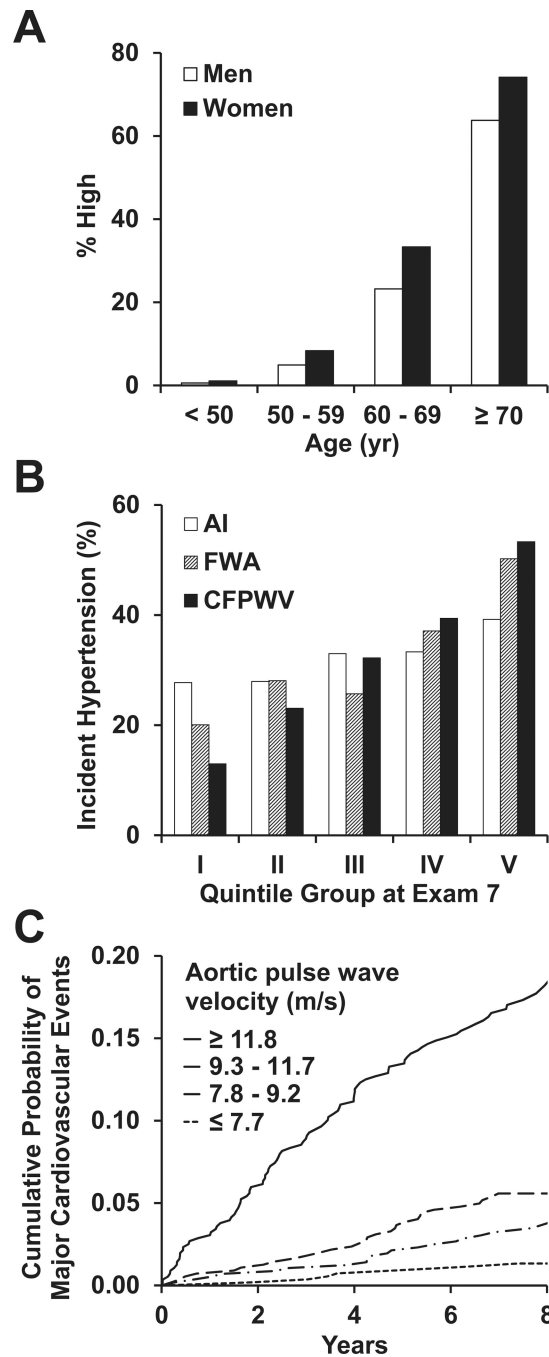
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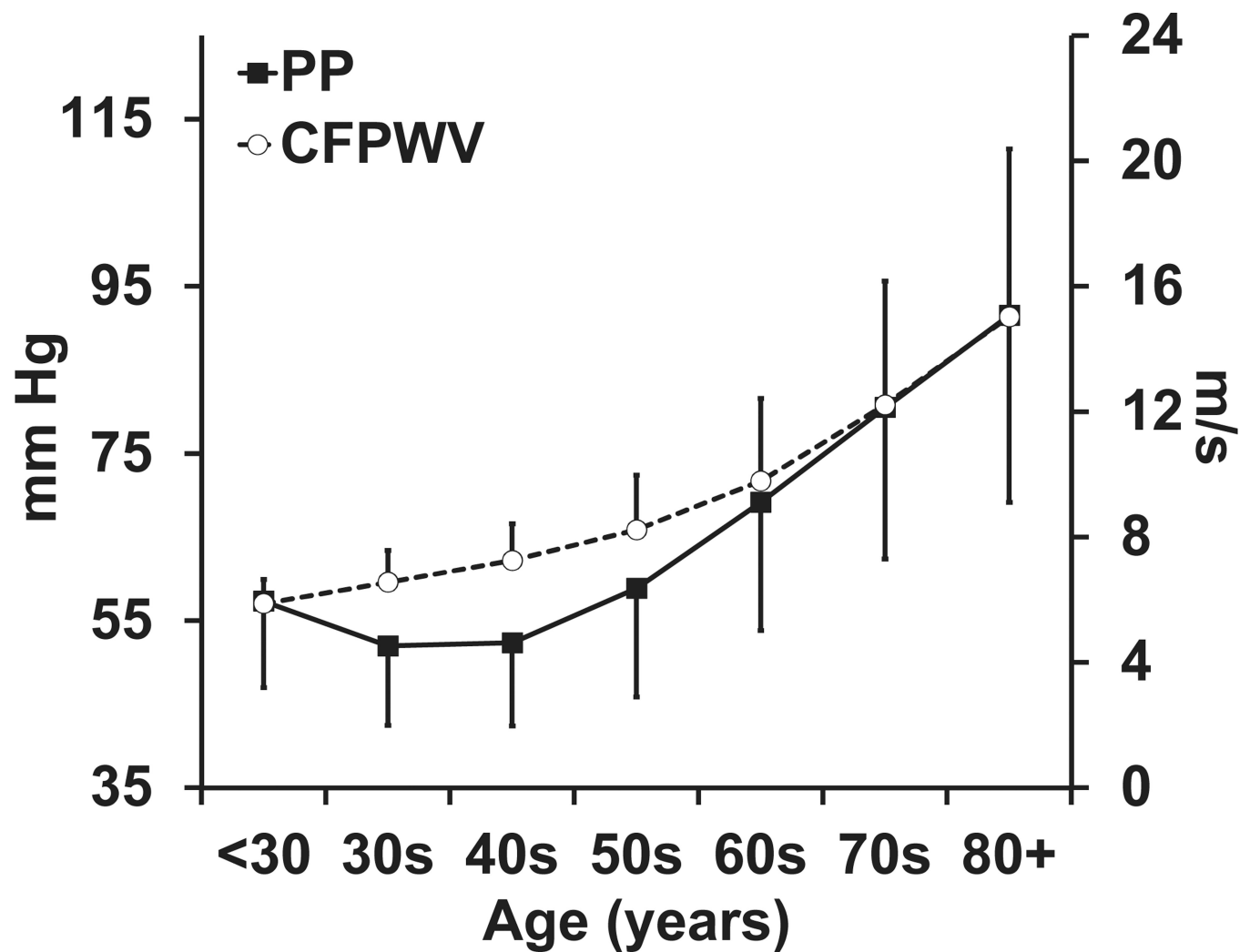
**Figure 1. Hypertension prevalence and control rates as a function of age in the National Health and Nutrition Examination Survey 2003–2004**

Data are derived from Wong, et al.<sup>44</sup>



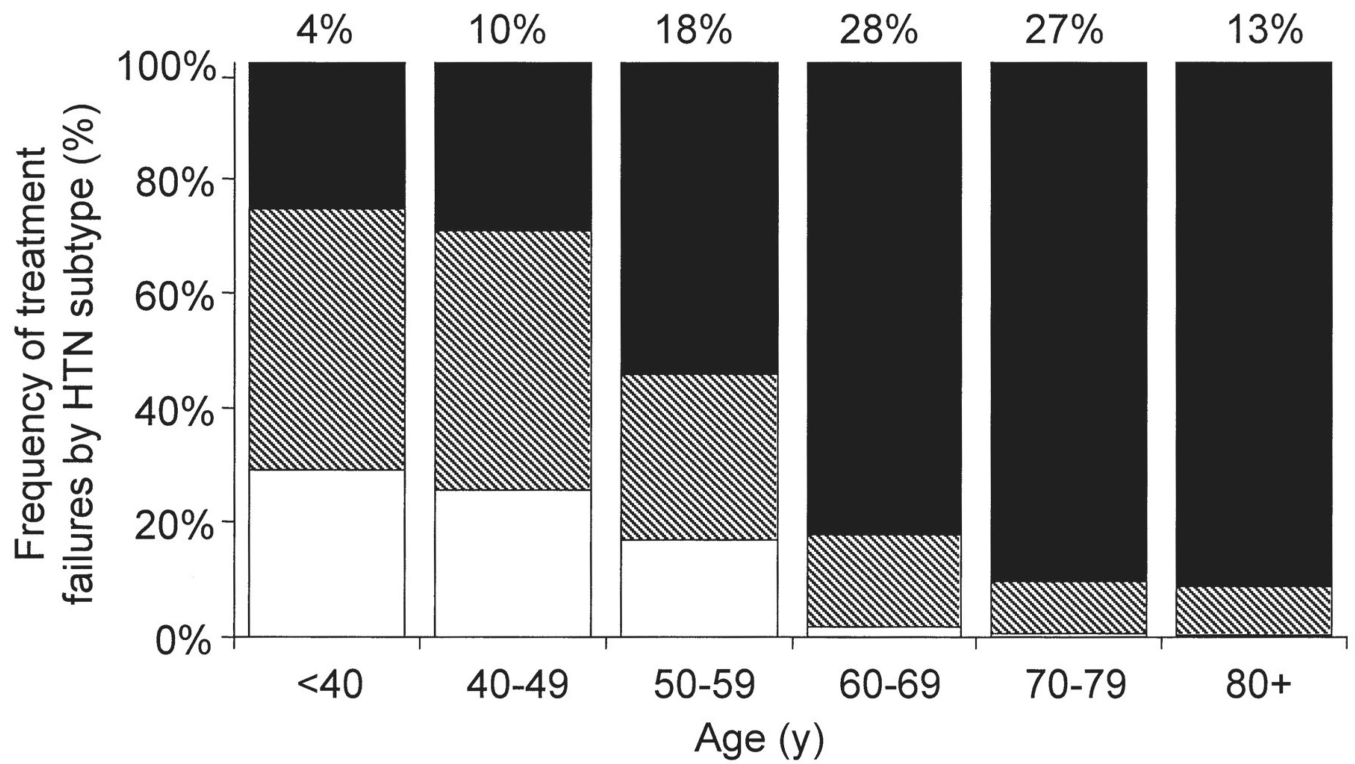
**Figure 2. Arterial stiffness, incident hypertension and cardiovascular disease**

**A.** The prevalence of a high-risk value for carotid-femoral pulse wave velocity ( $>12$  m/s) increases sharply from midlife to old age. **B.** The unadjusted risk for incident hypertension increases across groups defined according to quintiles of arterial stiffness (forward pressure wave amplitude, FWA, and carotid-femoral pulse wave velocity, CFPWV) and wave reflection (augmentation index, AI). **C.** The incidence of a first major cardiovascular disease event in groups defined according to quartiles of CFPWV in the Framingham offspring cohort. Reproduced from (A) Mitchell, et al.<sup>5</sup> (B) Kaess, et al.<sup>15</sup> and (C) Mitchell et al.<sup>32</sup>



**Figure 3. Mean values of pulse pressure (PP) and carotid-femoral pulse wave velocity (CFPWV) according to age in the Framingham offspring and third generation cohorts**

CFPWV increases monotonically with age, whereas PP falls with age in young adults through to midlife and then increases concordantly with CFPWV thereafter. The pattern of age associations suggest that progressive aortic wall stiffening antedates the onset of progressive widening of pulse pressure, which is a necessary precursor of wide-PP hypertension after midlife. Modified from Mitchell, et al.<sup>6</sup>



**Figure 4. Frequency of hypertension subtypes in patients with uncontrolled hypertension**

Beyond 60 years of age, isolated systolic hypertension was by far the leading subtype. White bars are isolated diastolic hypertension, hatched bars are mixed hypertension and black bars are isolated systolic hypertension. Reproduced from Franklin, et al.<sup>34</sup>