BU researchers with interests in this topic are encouraged to discuss their participation with Drs. Cohen and Morgan

With advancing age or prematurely in obese subjects, arterial stiffness increases and has been implicated in the altered vascular hemodynamics that ultimately lead to the development of hypertension\textsuperscript{1-5}. Stiffness begins in the aorta and large arteries, but because artery stiffness transmits higher pressures to the smaller resistance arteries, large artery stiffness is implicated in the microvascular complications of hypertension such as kidney disease and dementia. As the heart, kidney and brain receive the majority of the cardiac output, these are also the organs most damaged by hypertension, and by implication, the early effects of vascular stiffness. Thus, abnormalities in microvascular blood flow and function of each of these organs is associated with large artery stiffness. Data acquired at the Framingham Heart Study, a long-term community-based epidemiological study, indicate that vascular stiffness is an independent risk factor for cardiovascular disease endpoints. Arterial stiffness is assessed in patients by ultrasound measurements of pulse wave velocity (PWV). Figure 1 shows that subjects with increased arterial PWV have dramatically increased probability of major cardiovascular events including myocardial infarction and stroke\textsuperscript{6}. Because increases in PWV occur prior to hypertension, it has been proposed that routine measurements of PWV might provide an earlier, and therefore better predictor of cardiovascular disease and preventive treatments.

BUSM investigators have been at the forefront in defining a role for vascular stiffness as a determinant of cardiovascular risk in the community and performing epidemiological studies that have helped to establish a growing area of interest and importance as regards detection and prevention of cardiovascular disease\textsuperscript{4,5}. However, the fundamental mechanisms of arterial stiffness are not well established. These likely include altered properties of elastin and collagen that are recognized to increase vascular stiffness with aging, but also appears to include stiffness and increased tone of smooth muscle cells\textsuperscript{7}. Like increased smooth muscle tone, arterial stiffness may also be associated with endothelial dysfunction, another early predictor of cardiovascular disease \textsuperscript{8}. Thus, further investigations into the mechanisms of arterial stiffness will necessarily need to

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**Figure 1: Excess Cardiovascular Risk in FHS with Increased Pulse Wave Velocity**

![Figure 1: Excess Cardiovascular Risk in FHS with Increased Pulse Wave Velocity](image1)

**Mitchell GF, et al., Circulation. 2010;121:505-511.**

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**Figure 2: Pre-ARC on arterial stiffness, hypertension, and cardiovascular disease**

![Figure 2: Pre-ARC on arterial stiffness, hypertension, and cardiovascular disease](image2)
address the vascular biology of the arterial wall and its component cells - smooth muscle, endothelium, fibroblasts, and bone marrow derived cells.

The Arterial Stiffness Pre-ARC is being developed by a group of investigators interested in the structural, biochemical, physiological, molecular and genetic mechanisms that underlie arterial stiffness as it relates to negative cardiovascular disease outcomes (Figure 2). In part stimulated by a request for applications to address fundamental mechanisms of arterial stiffness issued by the NIH in the fall of 2009, our group started meeting to discuss related common interests and scientific expertise. The pre-ARC had monthly meetings at which investigators made presentations to familiarize others with their pertinent expertise. In addition, with the help of the Animal Ultrasound Core, directed by Dr. Victoria Herrera, the group has established the ability to assess PWV in rodent models of hypertension and arterial stiffness. At this writing, at least 4 such models including obese and aging mice/rats have been demonstrated to have increased arterial stiffness. Procedures are now in place to measure PWV in rodents being studied by faculty members who are interested in determining if their models of interest have increased arterial stiffness. Figure 3 shows an example of ultrasound imaging of the abdominal aorta of a 5 mm segment of mouse aorta and detection of the blood flow wave at each site. PWV is determined by measuring at each site the transit time (TT) of the flow wave from the peak of the R wave of the EKG. The PWV is calculated as the ratio of the difference in TT and distance between the two sites. The value obtained in normal mice (approx. 2 mm/mm/sec) is nearly the same as the normal value determined in children.

With the help of the Evans Center, in June 2009 the pre-ARC hosted a seminar and visit by Dr. Gary Mitchell, a Framingham investigator and leader in the field of arterial stiffness. Dr. Mitchell is currently evaluating correlates of arterial stiffness with cardiovascular disease endpoints and biomarkers in the Framingham cohort. This includes a multicenter, genome wide associations study of genetic polymorphisms that may correlate with stiffness. Pre-ARC members are actively pursuing a strategy by which rodent and biochemical models of interest can take advantage of new genetic findings based on arterial stiffness in people, for instance, determining the effects of altering the expression of genes found to be associated with stiffness, or comparing the genetics in rodent models in order to understand basic mechanisms.

Current members of the pre-ARC, all of whom either have, or are about to, discuss their interests in arterial stiffness at a pre-ARC meeting are listed below. Please contact the pre-ARC directors if you are interested in participating.

List of participating members:

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Prox. TT (ms)</th>
<th>Distal TT (ms)</th>
<th>Δt (ms)</th>
<th>Δd (mm)</th>
<th>Δd/Δt=PWV (mm/ms)</th>
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</thead>
<tbody>
<tr>
<td>Normal</td>
<td>17.25</td>
<td>19.50</td>
<td>2.25</td>
<td>5.13</td>
<td>2.28</td>
</tr>
</tbody>
</table>

Figure 3: Aortic Pulse Wave Velocity Measured in Mice

Proximal
Distal

Prox. TT 17.25 ms
Dist. TT 19.50 ms
References:


