Carotid Artery Vascular Mechanics Serve as Biomarkers of Cognitive Dysfunction in Aortic-Banded Miniature Swine That Can Be Treated With an Exercise Intervention

T. Dylan Olver, PhD; Diana Klakotskaia, MA; Brian S. Ferguson, PhD; Jessica A. Hiemstra, BS; Todd R. Schachtman, PhD; M. Harold Laughlin, PhD; Craig A. Emter, PhD

Background—Cognitive impairment in the setting of heart failure with preserved ejection fraction remains poorly understood. Using aortic-banded miniature swine displaying pathological features of human heart failure with preserved ejection fraction, we tested the hypothesis that increased carotid artery stiffness and altered carotid blood flow control are associated with impaired memory independent of decreased cardiac output. Furthermore, we hypothesized that chronic exercise prevents carotid artery vascular restructuring and preserves normal blood flow control and cognition in heart failure with preserved ejection fraction.

Methods and Results—Yucatan pigs aged 8 months were divided into 3 groups: control (n=7), aortic-banded sedentary (n=7), and aortic-banded exercise trained (n=7). At 6 months following aortic-banded or control conditions, memory was evaluated using a spatial hole-board task. Carotid artery vascular mechanics and blood flow were assessed at rest, and blood flow control was examined during transient vena cava occlusion. Independent of decreased cardiac output, the aortic-banded group exhibited impaired memory that was associated with carotid artery vascular stiffening, elevated carotid artery vascular resistance, and exaggerated reductions in carotid artery blood flow during vena cava occlusion. Chronic exercise augmented memory scores, normalized blood flow control, and improved indices of carotid artery vascular stiffening. Indices of vascular stiffening were significantly correlated with average memory score.

Conclusions—Carotid artery stiffness and altered vasomotor control correlate with impaired cognition independent of cardiac systolic dysfunction. Carotid artery vascular mechanics may serve as a biomarker for vascular cognitive impairment in heart failure with preserved ejection fraction. Chronic low-intensity exercise reduces vascular stiffening and improves cognition, highlighting the utility of exercise therapy for treating vascular cognitive impairment in heart failure with preserved ejection fraction. (J Am Heart Assoc. 2016;5:e003248 doi: 10.1161/JAHA.116.003248)

Key Words: carotid compliance • exercise training • experimental models heart failure • remodeling • vascular cognitive impairment

The term cardiogenic dementia describes the link between heart failure (HF) and cognitive dysfunction.1,2 Left ventricular (LV) systolic and diastolic dysfunction both appear to mediate the effect of HF on cognition. In HF with reduced ejection fraction (HFrEF), it is thought that reduced cardiac output (CO) leading to decreased cerebral blood flow3–5 and impaired autoregulation6,7 results in cerebral ischemia and subsequent cognitive decline.8,9 In contrast to HFrEF, the link between LV diastolic dysfunction (ie, HF with preserved ejection fraction [HFrEF]) and cognitive impairment (CI) remains unclear.10–12 Under resting conditions, patients with HFrEF exhibit normal CO and ejection fraction (EF) values,13,14 raising the question of whether the cerebral hypoperfusion hypothesis is valid for HFrEF patients. Among community-dwelling12 and hospitalized patients with HFrEF,11 the prevalence of cognitive dysfunction may be as high as 50% and explained, in part, by the severity of HF10 as well as noncardiac comorbidities including aging,12 chronic kidney disease, hypertension,11 and impaired glycemic control.15 Whereas standard HF therapies may attenuate the progression of cognitive decline in HFrEF,16 pharmacological treatments for HFrEF have proven largely ineffective.17 Limited evidence indicates that CI is a predictor of mortality at the...
initial diagnosis of HF and in hospitalized HFrEF patients and suggests the clinical relevance and importance of elucidating its contribution to developing disease.

In a joint position statement, the American Heart Association and the American Stroke Association indicated that carotid artery stiffness may serve as a therapeutic target for vascular CI. Arterial stiffness is a common feature of HFrEF that supports the idea that HFrEF is a total-body disease that is reflected in multiple organ systems, including peripheral vascular dysfunction, and is possibly mediated by a systemic inflammatory state. Furthermore, carotid artery stiffness correlates with decreased cerebral blood flow and cognitive dysfunction. CO and EF remain normal under resting conditions in HFrEF, and deficits in cognition may manifest as the result of peripheral vascular dysfunction. Consequently, carotid artery stiffness may serve as a clinical biomarker and/or therapeutic target for CI in HFrEF in the absence of impaired resting systolic cardiac function.

Using an aortic-banded miniature swine model displaying key pathological features of human HFrEF, including diastolic dysfunction, impaired contractile reserve, pathological cardiac remodeling, and lung congestion, we tested the hypotheses that increased carotid artery stiffness and altered control of carotid artery blood flow are associated with impaired spatial memory independent of decreased resting CO. Given the reported benefits of exercise training on indices of arterial stiffness and cognition, we also tested the hypothesis that a chronic low-intensity interval exercise intervention prevents carotid artery vascular restructuring and preserves normal blood flow control and cognition in an experimental setting of HFrEF.

**Methods**

**Study Design**

Sexually mature intact male Yucatan miniature swine (aged 8 months; N=21) were separated into 3 groups: (1) nonsham sedentary control (CON; n=7); (2) aortic-banded sedentary (AB; n=7) and (3) aortic-banded exercise trained (AB-EX; n=7). At 2 months after surgery, aortic banding significantly increased LV diastolic wall thickness (P<0.05; 5.8±0.5, 7.5±0.7, and 8.3±0.4 mm for CON, AB, and AB-EX, respectively) but did not alter LV end-diastolic dimension (P value not significant; 46.1±0.7, 44.3±1.3, and 43.9±1.4 mm for CON, AB, and AB-EX, respectively), indicating that concentric LV hypertrophy was present prior to the onset of exercise training. At 5 months after aortic banding, cognitive testing began and continued for 3 weeks. At 1 week following the end of cognitive testing, pigs were anesthetized and carotid artery vascular mechanics and blood flow control were examined. Experimenters were not blinded during the collection of cardiovascular outcome measures. All animal protocols were in accordance with the “Principles for the Utilization and Care of Vertebrate Animals Used in Testing Research and Training” and approved by the University of Missouri animal care and use committee.

**Aortic Banding**

Aortic banding was performed, as described previously. A 70-mm Hg trans-stenotic pressure gradient (74±2 and 74±1 for AB and AB-EX, respectively; P value not significant) was set under hemodynamically consistent conditions, defined as a peripheral vascular mean arterial pressure (MAP) of ≈90 mm Hg (90±1 and 91±1 for AB and AB-EX, respectively; P value not significant) set using phenylephrine (1–3 mg·kg⁻¹·IV) at a heart rate of ≈100 beats/min (103±5 and 99±8 for AB and AB-EX, respectively; P value not significant).

**Exercise Intervention**

At 2 months following aortic banding, pigs in the AB-EX group began exercise training 3 days per week for 18 weeks. Exercise consisted of low-intensity interval running performed on a motorized treadmill. Over the initial 4 weeks, pigs increased their workload gradually until each session consisted of (1) a 5-minute warmup at 2 miles per hour; (2) six 5-minute intervals at 3 miles per hour, with each 5-minute interval interspersed with a 3-minute interval at 4 miles per hour; and (3) a 5-minute cool-down period at 2 miles per hour.

**In Vivo Cardiovascular Function**

At 6 months following aortic banding, pigs were initially anesthetized using a mixture of Telazol (5 mg·kg⁻¹; Zoetis) and xylazine (2.25 mg·kg⁻¹) maintained using propofol (6–15 mg·kg⁻¹·min⁻¹ IV). At this dose, propofol does not impair cerebral autoregulation in pigs. Pigs were placed in the supine position, and heart rate (ECG), body temperature (rectal probe), and MAP (fluid-filled 6F arterial catheter) were monitored continuously. Total peripheral resistance was calculated as quotient of MAP relative to CO. Carotid artery vascular mechanics (%5 cm inferior to the carotid artery bifurcation) and blood flow (%2 cm inferior to the carotid artery bifurcation) were measured using Doppler ultrasound (Phillips HDI 5000). Data for vascular mechanics were averaged over 3 cardiac cycles, and data for blood flow were averaged over 10 cardiac cycles at baseline and 3 cardiac cycles during transient vena cava occlusion. Local mechanical properties of the carotid artery were calculated, as described previously.

Resting baseline carotid blood flow was calculated with a closed chest (ie, prior to the median sternotomy used to
perform pressure–volume loops) and measured as the product of the measured blood flow velocity and cross-sectional area of the carotid artery, as determined from the measured diameter. Shear rate was calculated as the product of 8 and the blood flow velocity, relative to the diameter of the carotid artery.\textsuperscript{34} Carotid artery vascular resistance was calculated as the quotient of MAP and carotid artery blood flow. Resistive index was calculated as the difference between peak systolic velocity and end-diastolic velocity relative to the peak systolic velocity.

Pressure–volume loops were collected, as described previously.\textsuperscript{28} A median sternotomy was performed, and a 5F admittance-based ADVantage catheter (Transonic Systems, Inc) was inserted into the left ventricle through a small apical incision. A 14F balloon occlusion catheter was inserted in the femoral vein and advanced to the inferior vena cava, and transient vena cava occlusion was achieved by inflating the balloon, during which time CO and peripheral MAP were monitored. Carotid artery blood flow was recorded at baseline, 5 seconds later, and at the end of vena cava occlusion. Cranial autoregulation was defined as the rate of regulation\textsuperscript{35} during transient vena cava occlusion and calculated as the rate of change in carotid artery vascular resistance relative to the change in MAP from baseline to 5 seconds. According to this definition, a rate of regulation of 5% s\textsuperscript{-1} indicates a per-second adjustment of 5% of the change necessary to compensate fully for changes in MAP.\textsuperscript{35} We were able to perform comprehensive hemodynamic, ultrasound, and pressure–volume loop analyses of 5 to 7 animals per group, and those are reported in each table for individual measures.

Cognitive Testing

Spatial hole-board recognition tasks (modified from Bolhuis et al\textsuperscript{36}) were performed in a 2\times6-m testing arena with 10 bowls placed in the form of a “U.” The entrance to the area was at the top of the U. The center of each bowl was 40 cm apart from the neighboring bowls. Three of the 10 bowls were baited with standard chow. To prevent visual cues, the bowls had removable lids, and the pigs were unable to see inside them. The pigs were able to open the lids with their snouts to gain access to the contents of the bowls. To prevent odor cues, all bowls contained a perforated grid with food placed above the grid in the 3 baited bowls and below the grid in the remaining 7 bowls.

After familiarization and standardization of trial performance among groups, exposure to the hole-board task was divided into 2 phases: (1) the acquisition phase and (2) the retention phase. The acquisition phase consisted of daily exposure to the spatial hole-board task for one 180-second trial (or until all food baits were located) for 5 consecutive days. The retention phase occurred 5 days following the last day of the acquisition phase and consisted of one 180-second exposure to the spatial hole-board task.

Scores for working memory (a form of short-term memory) were calculated as the ratio of the number of first-time visits to baited bowls to the total number of visits to baited bowls. Scores for reference memory (a form of long-term memory) were calculated as the ratio of the number of visits to the baited bowls to the total number of visits to all bowls.\textsuperscript{37} Scores were measured on all 5 days of the acquisition phase and during the retention phase. Average memory score was calculated as the mean of working and reference memory scores during the retention trial. To enhance motivation, pigs were fasted overnight, and testing took place between 6 and 8:30 AM in the fasted state. Between trials, the testing arena and the spatial hole-board task were washed with 30% ethanol. The order of testing was randomized, and experimenters were blinded to the experimental group during testing.

Statistics

Baseline vascular characteristics and differences in memory scores for the retention phase were compared using 1-way ANOVA. Hemodynamic variables during transient vena cava occlusion and memory scores during the acquisition phase were compared using mixed-model ANOVA (group \times time and trail, respectively). The location of significant interactions was determined using a post hoc Student Newman–Keul test. The Pearson correlation coefficient was calculated comparing carotid artery vascular mechanics versus average memory score for the retention phase. All data are reported as mean±SE, and significance is reported at $P<0.05$ levels.

Results

Cognitive Function

For the retention trial, working (short-term) memory scores were lower in AB versus CON pigs (Figure 1A). Working and reference (long-term) memory scores were greater in the AB-EX group compared with all other groups (Figure 1A and 1B).

Baseline Physical and Hemodynamic Characteristics

Body mass, EF, systolic and diastolic blood pressures, MAP, pulse pressure, and systolic and diastolic carotid artery diameters were similar between groups, and total peripheral resistance was increased in the AB group versus all other groups (Tables 1 and 2). Postmortem left ventricle plus
septum mass, ratio of left ventricle plus septum to end-diastolic volume, and end-diastolic pressure–volume relationship were all significantly increased in the AB and AB-EX groups versus CON (Table 2) and were observed in parallel to a strong trend toward increased diastolic septum wall thickness, indicative of concentric hypertrophy and impaired diastolic function. The Δ carotid artery diameter during the cardiac cycle was decreased in AB versus all other groups (Figure 2A). Carotid artery strain was reduced, and the Peterson elastic modulus was greater in AB versus all other groups (Figure 2B and 2C). Carotid artery stiffness was decreased, whereas distensibility and compliance were greater in AB-EX versus all other groups (Figure 2D through 2F). There was a trend toward decreased compliance in the AB versus CON group (P=0.09). Carotid artery blood flow and shear rate were reduced, and vascular resistance was greater in AB versus all other groups (Figure 3A through 3C). Resistive index was decreased in AB-EX versus all other groups.

Hemodynamics During Vena Cava Occlusion

CO was not significantly different between groups and decreased during vena cava occlusion in all pigs (Table 3). MAP was greater in the AB and AB-EX groups versus CON at baseline and at 5 seconds into vena cava occlusion but was similar between groups at the end of occlusion. Carotid artery blood flow was greater in AB-EX versus all other groups before and 5 seconds into vena cava occlusion; however, blood flow values were similar between groups at the end of occlusion (Table 3). There was a main effect of group for carotid artery vascular resistance, whereby vascular resistance was greater in the AB group versus all other groups and was lower in the AB-EX versus CON group (Table 3). The %Δ in CO decreased to a greater degree in the CON and AB groups versus AB-EX at 5 seconds, but the %Δ in MAP during vena cava occlusion did not differ between groups (Figure 4A and 4B). The %Δ in carotid artery blood flow decreased to a greater extent 5 seconds into vena cava occlusion in AB versus all other groups (Figure 4C). During vena cava occlusion, there was a main effect of group in which vascular resistance was greater at a given MAP in the AB group versus all other groups and was lower in the AB-EX versus CON group (Figure 4D). Furthermore, the rate of change in vascular resistance relative to MAP (ie, rate of regulation) was decreased in the AB group versus all other groups (Figure 4E).

Linear Regressions

All indices of carotid artery vascular mechanics were significantly correlated to average memory score.

![Figure 1. Working (A) and reference (B) memory scores during the retention trial phase. *P<0.05 vs all other groups; †P<0.05 AB vs CON. AB indicates the aortic-banded sedentary group; AB-EX, aortic-banded exercise-trained group; CON, nonsham sedentary control group.](image1)

![Table 1. Physical Characteristics and Peripheral Vascular Hemodynamics](table1)
during the retention phase. In addition, there was a significant negative correlation between carotid artery vascular resistance and average memory performance (Figure 5).

**Table 2.** ECG, Pressure–Volume Loop, and Postmortem Measures of Cardiac Parameters

<table>
<thead>
<tr>
<th></th>
<th>Control (n=5–7)</th>
<th>Aortic-Banded Sedentary (n=5–7)</th>
<th>Aortic-Banded Exercise Trained (n=5–7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ejection fraction, %</td>
<td>64±3</td>
<td>66±3</td>
<td>65±4</td>
</tr>
<tr>
<td>Septum wall thickness, mm</td>
<td>10.8±0.4</td>
<td>12.1±0.3*</td>
<td>11.8±0.5*</td>
</tr>
<tr>
<td>Left ventricle plus septum mass, g</td>
<td>140±6</td>
<td>171±6†</td>
<td>186±10†</td>
</tr>
<tr>
<td>End-diastolic volume, mL</td>
<td>105±11</td>
<td>103±9</td>
<td>103±7</td>
</tr>
<tr>
<td>Left ventricle plus septum to end-diastolic volume ratio</td>
<td>1.3±0.1</td>
<td>1.8±0.2†</td>
<td>1.7±0.1†</td>
</tr>
<tr>
<td>End-diastolic pressure–volume relationship, mm Hg/mL</td>
<td>0.005±0.001</td>
<td>0.011±0.002†</td>
<td>0.014±0.4†</td>
</tr>
</tbody>
</table>

*P=0.078 vs control.
†P<0.05 vs control.

**Discussion**

The current study examined whether the cognitive dysfunction often observed in HF is dependent on a decrease in CO and...
assessed the therapeutic effect of exercise training on this process in aortic-banded miniature swine. Our results revealed a number of novel findings. First, CI was evident in the AB group in the absence of a decline in resting systolic function (ie, resting EF percentage and CO were normal), implying that HF-induced dementia is not necessarily dependent on decreased CO. Second, cognitive dysfunction was strongly associated with increased peripheral vascular resistance, carotid artery stiffening, and impaired cranial blood flow responses during vena cava occlusion. Third, chronic low-intensity interval exercise training prevented cognitive and peripheral vascular dysfunction and improved carotid artery compliance despite chronic pressure overload at the level of the heart.

Cognition and Myocardial/Peripheral Vascular Function

The most interesting finding of the present study was that CI occurred independent of decreases in EF percentage or CO in AB animals. Carotid artery vascular stiffening, a characteristic often considered part of the HFrEF syndrome, occurred in conjunction with deficits in working memory, suggesting that carotid stiffness coincides with or predisposes patients with HFrEF to CI. Independent studies in human HFrEF patients reported carotid artery vascular stiffening and deficits in cognition.10–12 The current study furthers this previous work by unifying these separate observations in a translational large animal model reminiscent of human HFrEF. The AB group displayed lower cranial blood flow, elevated cranial vascular resistance, and exaggerated %Δ in carotid artery blood flow during vena cava occlusion, resulting in lower rate of regulation values. In contrast to HFrEF, these adjustments did not occur parallel to systolic dysfunction because resting CO was normal in the AB group. Consequently, peripheral vascular stiffening20–23 and augmented vasoconstriction,23,38 often observed in HFrEF and potentially related to reduced shear stress in the current study, likely contributed to the reduced resting carotid blood flow and impaired autoregulatory responses observed in AB animals. These results support our hypothesis and suggest that deficits in cognition manifest as the result of peripheral vascular dysfunction as opposed to myocardial systolic impairment. Furthermore, these findings provide additional support for the concept that HFrEF is a systemic disease affecting cardiac and noncardiac tissues alike.24,25

Clinical Significance

Given that arterial stiffness is characteristic of the HFrEF syndrome, the widespread clinical accessibility of high-resolution Doppler ultrasound highlights carotid artery vascular mechanics as an easily obtainable, reproducible, and potentially valid vascular biomarker, secondary to cognitive testing itself, for the purpose of tracking, preventing, or treating (vascular) CI in a setting of HFrEF. Recent position statements from the American
Regarding the clinical efficacy of exercise in a setting of diastolic dysfunction and LV remodeling, our results showed that chronic low-intensity interval exercise training improved indices of short- and long-term memory and prevented pathological carotid artery vascular restructuring in aortic-banded miniature swine. Exercise training appears safe, improves aerobic capacity and quality of life, and increases blood flow distribution to the frontal lobe during exercise in HFP EF patients. In this respect, the necessity of improving carotid artery stiffness to realize exercise-dependent improvements in health is unclear in HFP EF. In contrast to our findings, recent human studies have shown that neither pharmacological intervention nor exercise training (walking/upper and lower limb ergometry performed at 50–70% heart rate reserve, 3 days per week for 16 weeks) improves aortic or carotid artery stiffening. Furthermore, improved exercise capacity was not dependent on a reduction in carotid artery stiffness. The differences between our study and human findings could be a reflection of exercise intensity. The exercise intensity used by Kitzman and colleagues was relatively low compared with other studies in non-HFP EF populations that have documented exercise-induced reductions in arterial stiffness and may be less intense than our interval training paradigm. These differences outline the need to study exercise at variable intensities to optimize peripheral vascular function and overall exercise capacity in HFP EF patients.

The current study is, to the best of our knowledge, the first to demonstrate exercise-dependent benefits in cognition in a large animal experimental setting consistent with HFP EF. Exercise prevented carotid artery vascular stiffening, preserved normal blood flow control, and reduced the resistive index, indicating more continuous supply of blood flow to the head during diastole, perhaps the result of increased carotid artery and downstream microvascular compliance. Our findings reaffirmed the link between carotid artery vascular stiffening and CI and highlighted the therapeutic benefit of integrating exercise training into standard care for HFP EF patients at risk of developing CI. Combining our results with those in the literature clearly suggests that both cognitive dysfunction and exercise intolerance are, to a significant degree, the result of peripheral (vascular) dysfunction (as opposed to myocardial systolic impairment) and highlighted the potential clinical value of using carotid artery stiffness as a biomarker for CI in HFP EF patients. Furthermore, our results indicated that therapy targeted at improving peripheral conduit artery stiffness and possibly downstream compliance could be beneficial for improving HF-related dementia.

**Therapeutic Benefits of Chronic Exercise**

Regarding the clinical efficacy of exercise in a setting of diastolic dysfunction and LV remodeling, our results showed that peripheral arterial stiffness is an emerging marker of arterial aging that may also serve as a vascular risk factor for CI. Our regression analyses and ultrasound data support this conclusion because carotid artery stiffness, indicated by decreased arterial deformation, strain, and increased Peterson elastic modulus, was increased in the AB group and was significantly correlated with average memory scores. Although both HFP EF and HFr EF patients exhibit HF-induced CI, given that EF percentage and CO remain normal under resting conditions in HFP EF, our results suggested that deficits in cognition are the result of peripheral (vascular) dysfunction (as opposed to myocardial systolic impairment) and highlighted the potential clinical value of using carotid artery stiffness as a biomarker for CI in HFP EF patients. Furthermore, our results indicated that therapy targeted at improving peripheral conduit artery stiffness and possibly downstream compliance could be beneficial for improving HF-related dementia.

**Table 3. Hemodynamic Variables During Transient Vena Cava Occlusion**

<table>
<thead>
<tr>
<th></th>
<th>Cardiac output, L·min⁻¹</th>
<th>Mean arterial pressure, mm Hg</th>
<th>Carotid blood flow, mL·min⁻¹</th>
<th>Carotid vascular resistance, mm Hg·mL·min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (n=5)</td>
<td>Aortic-Banded Sedentary (n=6)</td>
<td>Aortic-Banded Exercise Trained (n=6)</td>
<td></td>
</tr>
<tr>
<td>Before</td>
<td>7.6±1.0</td>
<td>6.8±0.5</td>
<td>7.8±0.7</td>
<td>60±5‡</td>
</tr>
<tr>
<td>5 seconds</td>
<td>3.3±0.3</td>
<td>3.8±0.2</td>
<td>5.2±0.4</td>
<td>41±3‡</td>
</tr>
<tr>
<td>End</td>
<td>2.4±0.3</td>
<td>2.2±0.2</td>
<td>3.6±0.5</td>
<td>25±2‡</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>Before 60±5</td>
<td>80±7*</td>
<td>75±7*</td>
<td>28±1</td>
</tr>
<tr>
<td>5 seconds</td>
<td>41±3</td>
<td>60±5*</td>
<td>54±4*</td>
<td>31±3†</td>
</tr>
<tr>
<td>End</td>
<td>25±2</td>
<td>31±3</td>
<td>28±1</td>
<td></td>
</tr>
<tr>
<td>Carotid blood flow, mL·min⁻¹</td>
<td>Before 239±31</td>
<td>288±33</td>
<td>441±55§</td>
<td></td>
</tr>
<tr>
<td>5 seconds</td>
<td>192±31</td>
<td>183±26</td>
<td>352±42‡</td>
<td></td>
</tr>
<tr>
<td>End</td>
<td>78±8</td>
<td>76±11</td>
<td>116±11</td>
<td></td>
</tr>
<tr>
<td>Carotid vascular resistance, mm Hg·mL·min⁻¹</td>
<td>Before 0.26±0.01</td>
<td>0.29±0.02‡</td>
<td>0.18±0.02§</td>
<td></td>
</tr>
<tr>
<td>5 seconds</td>
<td>0.23±0.02</td>
<td>0.34±0.02‡</td>
<td>0.16±0.01†</td>
<td></td>
</tr>
<tr>
<td>End</td>
<td>0.34±0.04</td>
<td>0.44±0.06‡</td>
<td>0.25±0.02‡</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.05, group–occlusion interaction, aortic-banded sedentary and exercise trained vs control.

†P<0.05, group main effect, aortic-banded sedentary vs all other groups.

‡P<0.05, group main effect, aortic-banded exercise trained vs all other groups.

§P<0.05, group main effect, aortic-banded exercise trained vs control.

Heart Association and the American Stroke Association stated that peripheral arterial stiffness is an emerging marker of arterial aging that may also serve as a vascular risk factor for CI. Our regression analyses and ultrasound data support this conclusion because carotid artery stiffness, indicated by decreased arterial deformation, strain, and increased Peterson elastic modulus, was increased in the AB group and was significantly correlated with average memory scores. Although both HFP EF and HFr EF patients exhibit HF-induced CI, given that EF percentage and CO remain normal under resting conditions in HFP EF, our results suggested that deficits in cognition are the result of peripheral (vascular) dysfunction (as opposed to myocardial systolic impairment) and highlighted the potential clinical value of using carotid artery stiffness as a biomarker for CI in HFP EF patients. Furthermore, our results indicated that therapy targeted at improving peripheral conduit artery stiffness and possibly downstream compliance could be beneficial for improving HF-related dementia.
American Stroke Association indicate that models in higher order species are needed and desirable, given the limitations of rodent models in terms of small amounts of white matter and behavioral range. Both pig brain and heart share similar anatomical, biochemical, and functional similarities with those of humans, including brains that are gyrencephalic, that contain >60% white matter, and that rely primarily on the carotid and middle cerebral arteries for continuous blood supply. These features make the pig ideal for studying the relationship between peripheral/cerebral vascular function and cognition in terms of optimizing translational impact.

Considerations

Blood flow was measured in the common carotid artery, which supplies the entire head and not the cerebral circulation exclusively. The depth and steep angle of the pig internal carotid artery rendered it impossible to obtain valid measures using Doppler ultrasound at an angle of insonation <60°. To ensure the most accurate, valid, and reproducible values, we examined the common carotid artery overestimates cerebral flow, but flow in the 2 vascular segments exhibits a strong correlative relationship ($R=0.94$). Given that alterations in blood flow through the common carotid artery may arise from changes in downstream vascular control in the skin, muscle, or brain, we ensured that body temperature remained stable and skeletal muscle remained inactive throughout the protocol. Advantages of examining the common carotid artery using Doppler ultrasound rest on its easy accessibility and high degree of reproducibility as well as its widespread clinical use.

DOI: 10.1161/JAHA.116.003248

Figure 4. Percentage changes in (A) cardiac output, (B) mean arterial pressure, and (C) carotid artery blood flow; (D) changes in carotid artery vascular resistance ($^\dagger P<0.05$, group main effect, AB vs all other groups, $^\ddagger P<0.05$, group main effect, CON vs AB-EX); and (E) RoR at 5 seconds and the end of vena cava occlusion. $^* P<0.05$ vs all other groups. AB indicates the aortic-banded sedentary group; AB-EX, aortic-banded exercise-trained group; CON, nonsham sedentary control group; RoR, rate of regulation.

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Although our data support a link between peripheral vascular dysfunction and CI in a large animal model reminiscent of stable human HFpEF, they do not definitively demonstrate that CI was caused by peripheral conduit artery dysfunction alone. It is also important to note from an epidemiological perspective, compared with the current animal model, that humans with HFpEF tend to be older women that exhibit multiple comorbidities, including advanced age and type 2 diabetes. Although a primary strength of our study is the use of in vivo methodology in a large animal model that provides translational impact, it limits our sample size. In total, these important perspectives underscore the importance of examining these findings in human HFpEF to validate the clinical relevance of our study.

**Conclusion**

We provided evidence that elevated carotid artery stiffness, cranial hypoperfusion, and impaired blood flow control are associated with deficits in cognition independent of cardiac systolic dysfunction at rest in aortic-banded miniature swine. Furthermore, chronic low-intensity interval exercise training...
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prevented cognitive dysfunction while preserving normal blood flow control and improving clinical indices of carotid arterial stiffness. In contrast to HFrEF, these findings suggest that HFP EF-induced dementia stems from peripheral (vascular) dysfunction and support the use of carotid artery stiffness as a biomarker and/or risk factor for cognitive dysfunction in HFP EF.

Acknowledgments

We would like to thank Jan Ivey, Melissa Cobb, and Pam Thorne for their technical assistance in completing this project. We would also like to thank Gore for their generous gift of vascular Gore-Tex sleeves used in our aortic-banding procedures.

Sources of Funding

This work was supported by RO1 HL112998, PI: Emter.

Disclosures

None.

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DOI: 10.1161/JAHA.116.002248

Journal of the American Heart Association


37. van der Staay FJ, Gieling ET, Pinz


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*J Am Heart Assoc.* 2016;5:e003248; originally published May 20, 2016; doi: 10.1161/JAHA.116.003248

The *Journal of the American Heart Association* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Online ISSN: 2047-9980

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