Exercise as an Antihypertensive Intervention; Does Mode and Gender Matter?

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Hypertension (HTN)

- Stage -1 Essential Hypertension
  - SBP > 140 mmHg
  - DBP > 90 mmHg

- Undetected chronic elevated BP increases a person's risk of developing cardiovascular disease and stroke by 3- and 7-fold, respectively

Campbell et al. 1999
Pre-Hypertension

- SBP > 120 mmHg
- DBP > 80 mmHg

Self-accelerating condition where evolving arteriolar hypertrophy and endothelial dysfunction facilitate the later transition of pre- to essential HTN.
Untreated Hypertension

- Considered a precursor of stage-1 essential hypertension
- Associated with excess morbidity and deaths from cardiovascular causes.

Folkow, 1982
Treatments

- Antihypertensive Drugs
- Psychotherapy
- Exercise
Drugs

- Trial Of Preventing Hypertension (TROPHY) examined whether the treatment of prehypertension may delay the development of HTN

- 4 year, multicenter randomized study of untreated pre-hypertensive subjects

*NEJM, 2006*
Design

- **Subjects**
  - n = 722, ages 30-65 yrs (mean = 49)
  - **391 candesartan** (Blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1) vs. **381 placebo**

- **Methods**
  - 2 years dosing with ARB
  - 2 year BP follow-up
**No. of Patients without Hypertension**

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>391</td>
<td>356</td>
<td>309</td>
<td>191</td>
<td>127</td>
</tr>
<tr>
<td>Placebo group</td>
<td>381</td>
<td>269</td>
<td>184</td>
<td>118</td>
<td>85</td>
</tr>
</tbody>
</table>
Concluded

- Pharmacologic treatment of pre-hypertension may prevent or postpone the development of hypertension (26% reduction of new onset in drug group vs. placebo)
Pharmacological risk

- Exposes 25 million Americans to the prospective health risks and patienthood and have an enormous economic impact on the public healthcare system.

  Grassi DG, 2006

- Skeptical results since the post-treatment period for the intervention and control groups were biased with the pre measures.
Aging and Antihypertensives

- With increasing age, irreversible damage (i.e. changes in the vasculature due to hypertrophy or atherosclerosis) may diminish the long term responsiveness to temporary antihypertensives

Levy et al., 1990 and Stokes et al. 1987
Increasing incidence of HTN and CVD

- Directly related to changes in lifestyle and diet considerations

- Earlier onset of drug therapy will not solve the problem if obesity and sedentary lifestyle choices continue to increase

Grassi DG, 2006
Exercise

- Low cardiorespiratory fitness is a strong and independent predictor of CVD and all-cause mortality

- It is well established that higher activity levels equates to higher cardiorespiratory fitness and lower blood pressures

- Exercise can be an antihypertensive lifestyle modification to help prevent/control BP

Wei et al. 1999
Exercise reduces risk factors

- Meta-analyses of exercise-based cardiac rehab (contemporary meds/interventions era) estimate a reduction in mortality of 20-32%
  
  Taylor et al., 2004

- Exercise is associated with ~30% benefit in terms of cardiac risk (similar to lipid lowering and antihypertensive interventions)

Reduction of risk

- It is proposed by Green et al. (2008) that the direct effects of exercise offer cardioprotection on the vascular wall conferring a “vascular conditioning” effect.
Aerobic Exercise Training

- Aerobic exercise training at moderate intensity has been shown to decrease RBP of individuals w/HTN
  - SBP 8-17 mmHg
  - DBP 6-13 mmHg
THE SATURDAY EVENING POST

APRIL 29, 1922

In This Number
GEORGE PATTULLO - DANA BURNET - MARGUERITE CURTIS
RICHARD CONNELL - EVERETT RHODES CASTLE - JULIAN STREET

The Bodybuilder, Post cover, 1922.
Resistance Exercise Training

- Nine studies have investigated the resting BP responses to resistance exercise training (144 exercise vs. 115 control) in adults

- Mean reduction in resting SBP of 4.6 ± 1.75 and a resting DBP reduction of 3.8 ± 1.5 mmHg
Resistance Training

- Resistance training is only recommended as a “complement” to an aerobic based exercise program (AHA, 2005)
  - Fast
  - Increases BMD if done correctly
  - Contraindications
Mode of Training

- Resistance Training leads to decreases in BP, yet increases in HR and arterial stiffness
Endothelium
Large Elastic Artery
Stiff Artery
Pulse Wave Velocity
Methodology

- 30 Pre-hypertensive to Stage 1 essential hypertensive subjects (20 Men 10 Women)
- No medications
- Lab familiarization
  - Informed Consent and medical history forms
  - Body Composition
  - Randomization (4 weeks of either RT or AT)
  - $\text{VO}_{2\text{peak}}$ or 10RM testing
Methods

- Visit 2 Baseline testing
- IHP familiarization

15 min. supine rest

- PWV
- B2B
- BF and RH
Exercise Training

- **AEROBIC**
  - Treadmill
  - 65% VO2max (HR)
  - 30 minutes
  - 3 days/week

- **RESISTANCE** 3 sets, 1 minute rest
  - LifeFitness machines
    - Leg press
    - Lat pulldown
    - Leg extension
    - Chest Press
    - Leg curl
    - Shoulder press
    - Bicep curl
    - Tricep press
    - Abdominal crunch
## Subjects

<table>
<thead>
<tr>
<th></th>
<th>AEROBIC</th>
<th>RESISTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.8 ± 1.6</td>
<td>47 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.2 ± 2.7</td>
<td>172.5 ± 2.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>86 ± 5/ 85 ± 5</td>
<td>90 ± 5/ 90 ± 5</td>
</tr>
<tr>
<td>BMI (wt/ ht²)</td>
<td>29 ± 1.8</td>
<td>30 ± 1.2</td>
</tr>
<tr>
<td>Body fat %</td>
<td>32.9 ± 2.3</td>
<td>31.8 ± 1.7</td>
</tr>
</tbody>
</table>
## BP Results

<table>
<thead>
<tr>
<th></th>
<th>AEROBIC</th>
<th>RESISTANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>SBP</td>
<td>141.2 ± 3.4</td>
<td>136.6 ± 3.4 *</td>
</tr>
<tr>
<td>DBP</td>
<td>80 ± 1.47</td>
<td>76.9 ± 1.63 *</td>
</tr>
<tr>
<td>MAP</td>
<td>103.5 ± 1.8</td>
<td>100.3 ± 2 *</td>
</tr>
<tr>
<td>HR</td>
<td>72.5 ± 2.9</td>
<td>67.5 ± 2.8 *†</td>
</tr>
</tbody>
</table>
Central PWV Results

- **Aerobic**
  - PRE: 9 m/s, POST: 10 m/s (significant decrease)

- **Resistance**
  - PRE: 13 m/s, POST: 14 m/s (significant increase)

* indicates a significant difference.
Peripheral PWV

<table>
<thead>
<tr>
<th></th>
<th>PRE</th>
<th>POST</th>
</tr>
</thead>
<tbody>
<tr>
<td>PWV</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>

Aerobic: Significant decrease (*)

Resistance: No significant change
Is it arterial remodeling?

- Collier et. al MSSE 2006
- We showed that distensibility decreases following an acute resistance training bout and returns to pre-exercise levels in about 60 minutes
- Functional remodeling
Baroreflex Sensitivity Results

- **Resistance**
- **Aerobic**

**PRE** vs. **POST**

* indicates a significant difference.
Forearm Blood Flow Results

**Aerobic**

- Resistance

PRE

POST

FBF (ml \cdot 100 ml \cdot min^{-1})

*
Post Ischemic Forearm Peak Flow

Aerobic

Resistance

*  

Peak FBF

(ml · 100 ml⁻¹ · min⁻¹)

PRE

POST

*
Post Ischemic AUC Blood Flow

AUC (ml · 100 ml⁻¹ · min⁻¹)

PRE    POST

*  

Aerobic
Resistance
## Absolute values - Autoregressive Model

<table>
<thead>
<tr>
<th></th>
<th>AEROBIC</th>
<th></th>
<th>RESISTANCE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n=10 males; 4 females</td>
<td></td>
<td>n=10 males; 5 females</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
</tr>
<tr>
<td>LF (m·sec$^2$)</td>
<td>526.64 ± 220.09</td>
<td>498.29 ± 180.96</td>
<td>670.20 ± 212.63</td>
<td>801.60 ± 74.82</td>
</tr>
<tr>
<td>HF (m·sec$^2$)</td>
<td>287.93 ± 143.29</td>
<td>528.71 ± 392.34</td>
<td>654 ± 138.43</td>
<td>1153.40 ± 379.04</td>
</tr>
<tr>
<td>nLF (m·sec$^2$)</td>
<td>0.55 ± 0.055</td>
<td>0.53 ± 0.06</td>
<td>0.525 ± 0.06</td>
<td>0.54 ± 0.06</td>
</tr>
<tr>
<td>nHF (m·sec$^2$)</td>
<td>0.42 ± 0.06</td>
<td>0.50 ± 0.06</td>
<td>0.46 ± 0.06</td>
<td>0.45 ± 0.05</td>
</tr>
<tr>
<td>TP (m·sec$^2$)</td>
<td>1234.2 ± 718.97</td>
<td>1626.0 ± 936.34</td>
<td>2842.73 ± 694.10</td>
<td>3601.73 ± 904.59</td>
</tr>
<tr>
<td>LF:HF ratio</td>
<td>2.75.21 ± 93.43</td>
<td>161.26 ± 51.99</td>
<td>143.37 ± 24.00</td>
<td>227.83 ± 66.81</td>
</tr>
</tbody>
</table>

Collier et al *Acta Physiologica* - 2009
Conclusions

- Similar reductions in resting BP for both training modes.

- 4 weeks of moderate intensity resistance training increased arterial stiffness while aerobic exercise training decreased arterial stiffness.

- Significant increases in peak and AUC forearm blood flow, in response to RH, increased vasodilatory capacity, however, these changes were greater in the resistance trained group.
Conclusions

- Training induced changes in arterial stiffness appear to be unrelated to changes in BP, vasodilatory capacity and body weight
Sex differences

- Women demonstrate the greatest increase in CVD prevalence with advancing age.
- Approximately 35-40% of women aged 55-65 years with CVD reported to be disabled by their illnesses.

*Eaker, 1993 and Davy, 1987*
Sex Differences

- Hypertension is more prevalent and less well controlled and more severe in elderly women than in men.

- Differences may be related to higher HR and earlier reflected pulse waves which lead to the development of greater SBP, PP and DBP.
Appropriate pharmacological treatment is controversial as a recent meta analysis has shown antihypertensive drugs are less beneficial for women.
Sex Differences in Resting Hemodynamics and Vascular Distensibility Following Resistance Exercise Training in Hypertensives

- 4 weeks of AE and RE on resting hemodynamics and arterial distensibility in 34 age-matched pre-stage 1 essential hypertensives.

Collier et al., FASEB (S) 2008
## BP results

<table>
<thead>
<tr>
<th></th>
<th>Aerobic</th>
<th></th>
<th>Resistance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>SBP * (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>136 ± 3.5</td>
<td>131 ± 2.9</td>
<td>132 ± 2.9</td>
<td>128 ± 2.4</td>
</tr>
<tr>
<td></td>
<td>147 ± 5.5</td>
<td>143 ± 6.4</td>
<td>148 ± 7.3</td>
<td>142 ± 8.5</td>
</tr>
<tr>
<td><strong>DBP * (mmHg)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 ± 3.5</td>
<td>76 ± 3.5</td>
<td>78 ± 3.5</td>
<td>76 ± 3.5</td>
</tr>
<tr>
<td></td>
<td>81 ± 2.5</td>
<td>78 ± 2.6</td>
<td>78 ± 3.2</td>
<td>68 ± 3.4</td>
</tr>
</tbody>
</table>

*n = 21 M and 13 F*
PWV res

PWV (m/s)

PWV pre  PWV post

Male

Female

*
Results

- Both modes significantly reduced resting SBP and DBP
- In contrast, RE significantly increased PWV in men, but had no effect in women
Conclusion

- These data suggest that both sexes would benefit from the BP-lowering effects of RE but that hypertensive women have an added advantage compared to men, that RE does not increase arterial stiffness.
Sex Differences

- Aging – Does exercise have the same anti-hypertensive effects at any age?
- What is the mechanism (post menopausal so no Estrogen)
- The role of renin and other hormones?
Hormones of interest

- **Renin** – overexpressed in hypertensives, cleaved into angiotensin-1
- **Angiotensin** – attenuates baroreflex control of HR
- **Leptin** – signaled out of adipose tissue, may be a direct mechanism of elevated blood pressure
Renin

- The Renin-Angiotensin-Aldosterone System (RAAS) is a strong modulator of the arterial system.

- Over expression of renin leads to increased vasoconstriction → inc. PWV
Renin and Aging

- Neurohumoral systems modulate the RAAS and increase sympathetic tone which in turn contributes to age-related BP increases

Izzo, 2007
Obesity and Blood Pressure

- The hemodynamic changes we found are consistent with exercise induced weight loss

- Mechanisms could be the same

- Intervention should be the same?
Obesity Study Methodology

- Control wait period of 4 weeks for 5 subjects

- Subjects
  - BMI greater than 30
  - No medications

- Blood draws to look at hormone and plasma volume changes

Carta and Collier, *FASEB*, 2008
Results

- n=34
- While mode of exercise did have an effect on arterial distensibility (RE increased stiffness and AE decreased stiffness), age and obesity status did not show a significant effect.

- Further, AE and RE both lowered resting BP significantly with no difference between mode.
Leptin

- Product of the obesity gene, exerts a myriad of effects on many tissues
- Over expression of Leptin augments sympathoexcitation
- Augments vasoconstriction in the periphery leading to increased vascular resistance

Knudson, 2005
Hyper Leptinemia

- Plasma leptin concentration positively correlates with adiposity

- Hyperleptinemia is an independent risk factor for coronary artery disease and a strong predictor of MI and causes platelet aggregation and thrombosis
Leptin receptors

Human long-form leptin receptor (ObRb) is expressed in human coronary artery endothelial cells.
Leptin is tied to BP regulation during sleep

Schmid, 2006
Renin and Sleep

- The renin-angiotensin aldosterone system (RAAS), mainly via production of angiotensin II (Ang II), is a key regulator of BP.

- Renin secretion is activated in the early morning before arousal as a result of sympathetic neuronal activation

White WB, 2007
Dipping of BP at night

Sayk, Hypertension 2007
Exercise and hormone expression

- Does the decreases in BP following exercise training mimic changes in hormone levels?

- Does the timing of exercise prior to sleep modulate leptin/renin secretion?

- Can we alter non-dippers with exercise?
Thank You