Sleep Apnea induced Endothelial Dysfunction: could it be reversible?

Q: What is Endothelial Dysfunction?
1. normal anatomy of blood vessels

Dysfunction begins with an endothelial insult such as:
- increased shear stress damage
- bacterial adherence
- oxidative stress = reactive oxygen/nitrogen species
- expression of pro-inflammatory mediators

Scanning Electron Microscope

Macrophages sticking to endothelium
Q: How can we measure Endothelial Dysfunction?
3. Markers of Endothelial Dysfunction
   A. Cardiovascular/Cardiac Function
      Hypertension
      HRV & Arrhythmia
   B. Serologic Markers
      C-reactive protein; Cytokines
      High Density Lipoproteins
      ROS (Peroxidase)
   C. Provocation Testing
      Flow Mediated Dilation (FMD)
      Peripheral Arterial Tonometry

A. Hypertension, HRV & Arrhythmia

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B. Serologic Markers of Arterial Disease

C-Reactive Protein (CRP) is a protein found in the blood that is produced in the liver in response to infection, cancer & inflammatory diseases.

Proinflammatory cytokines promote systemic inflammation (e.g. IL-1 or TNF-alpha)

Peroxidases are a large family of enzymes that typically catalyze a reaction (e.g. lipid peroxides).
Click here to watch a 9 minute video on Flow Mediated Vasodilation Testing
https://www.youtube.com/watch?v=YlfVcp65cwE

C. Provocation Testing
(Brachial Artery Flow-Mediated Vasodilation)

Takase B, Am J Cardiol 1998;82:1535
Comparison of Brachial and Coronary Flow-Mediated Vasodilation
Peripheral Arterial Tonometry

Q: Does increased arterial stiffness predict cardiovascular disease?

Schachinger V et al, Circulation 2000;101:1899

Rate of CVE's over 7.7 Years in 147 Subjects with CAD grouped by FMD

[Bar chart showing the rate of CVE's over 7.7 years in 147 subjects with CAD grouped by FMD]
Q: Is Endothelial Dysfunction related to obstructive sleep apnea?
4. Association between SDB and ED

Three studies on hypertension, CV function & OSA:
Data show that with OSA there is increased:
1) sympathetic nerve activity
2) serologic markers of endothelial activation
3) markers of carotid atherosclerosis
4) elevated heart rate variability
5) morning elevated diastolic blood pressure


Three studies on serum inflammatory markers & OSA:
Data show that with OSA there is increased:
1) C-reactive protein levels associated with ODI > 10
2) Untreated SDB (ODI>20/h) associated with CRP
3) Moderate/severe OSA associated with low HDL-cholesterol serum levels in the elderly.

Click here to watch a 6 minute video on CPAP Risk and Benefits
https://www.youtube.com/watch?v=CAa23cBegcY

Q: Does CPAP reverse endothelial dysfunction?

Meta-analysis of CPAP effect on arterial stiffness in OSA
1. 15 studies (n=615) assessed arterial stiffness and CPAP
2. 5 different meta-analyses were performed

Results:
1. significant improvement of all arterial stiffness after CPAP
2. Compliance with CPAP did not alter result

Conclusion: meta-analyses showed significant improvements in all indices of arterial stiffness after CPAP treatment in patients with OSA.

Q: Does a MAD reverse endothelial dysfunction?

Five studies on MAD tx and HTN in OSA:
Data show that with MAD tx:
1) MAD tx for 4 wks lowered 24 hr DBP slightly
2) MAD tx lowered daytime blood pressure.
3) MAD tx reduced DBP at 3-m and 3-yr point

16 subjects (11m/5f).
- mean age = 54.0±8.3/y
- BMI = 28.0±3.1 kg/m²

Venous blood (10 ml) samples obtained from each patient after an overnight fast for purpose of testing the biochemical markers of oxidative stress.
Peripheral Arterial Tonometry Probe

Testing with PAT

Provocation testing (PAT) & MAD Tx:
Data shows that the MAD (Herbst):
1. Reduces AHI, ODI and Sleepiness scores
2. Reduces Serologic Markers of Inflammation
3. Reduces Arterial Stiffness
   (at the 3 months and the 1 year tx point)

**Implication of Data**

Improved EF (back to normal levels) without a complete elimination of apneic events suggesting there is a threshold for episodic hypoxia on EF.

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**Q: Since Itzhaki (2007) has this result been validated?**

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Study: MAD effect on arterial stiffness & inflammatory markers.
1. 18 patients with mild to moderate OSA enrolled
2. MAD treatment effect at 3 months and 1 year
3. PSG, arterial stiffness and blood test for markers
4. 1 year data were compared to baseline values.

Results:
1. Significant decrease in AHI at 1 yr (22.9±5.9 to 9.7±4.5)
2. Reduce fasting plasma glucose at 1 yr (5.3±0.5 to 4.9±0.5)
3. Plasma level of inflammatory marker fibrinogen decreased significantly from 3.4 ± 0.7 at baseline to 3.0 ± 0.9.

**Conclusions:** MAD Tx improved arterial stiffness, glucose metabolism and fibrinogen levels in OSA patients at 1 year.
Conclusions

1. Atherogenic disease (in part) occurs due to oxidative stress associated with chronic intermittent hypoxia (OSA).
2. Finally arterial inflammation (evidenced by serologic markers of inflammation) is related to OSA because hypoxia –reoxygenation during sleep produces reactive oxygen species (ROS) which damages the endothelium.
3. Treatment both with CPAP (>5hr/n) and MADs can reverse some of this damage.

The End!

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