UNIVERSITY OF MIAMI HEALTH SYSTEM

UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE Effectiveness of beta blocker therapy in pediatric patients with orthostatic intolerance and abdominal complaints and reduced superior mesenteric artery flow during head-up tilt

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I have nothing to disclose



Orthostatic intolerance is a term used to describe symptoms associated with maladaptive circulatory response to upright posture (POTS, NMH, Reflex)

Tilt testing enables the reproduction of neurally mediated reflex in laboratory settings. It triggers hypotension and usually concomitant heart rate slowing, related to impaired vasoconstrictor capability followed by sympathetic withdrawal and vagal over activity



- Gastrointestinal (GI) symptoms are common in patients with orthostatic intolerance (OI).
- Sullivan et al (2005) reviewed the charts of pediatric patient with abnormal HUT results referred to GI clinic with abdominal complaints.
 - Most common presenting symptoms were:
 - Abdominal pain (71%)
 - Nausea (56%)
 - Vomiting (50%)
 - Additional symptoms included diarrhea, weight loss, anorexia and heart burn



Studies performed by Perko M.J. et al, in 1997-1998 showed that in normal adults:

- Head-up tilt (HUT) reduces cardiac stroke volume (by inducing central hypovolemia) and induces hypotension when maintained for ~30 minutes.
- Simultaneously, SMA impedence decreases, but the blood flow is maintained.



<u>Conductor</u>

 $V = I \times R$

- I is the current through a conductor
- V is the voltage measured across the conductor
- R is the resistance of the conductor

Superior Mesenteric Artery

BP = Flow x Resistance

- I is the blood flow through the SMA
- V is the BP across the SMA
- R is the resistance of the SMA



Regulatory mechanisms for SMA response to HUT are not well known, but there is an increase in vagal activity.

Increase in vagal activity can elevate mesenteric blood flow by direct vasodilator action of acetylcholine and by the release of vasodilator substances

Perko, MJ., Madsen, P., Perko, G., Schroeder, T.V., & Sechner, N.H. 1997a. Mesenteric artery response to the head-up tilt induced central hypovolaemia and hypotension. Clin Physio 17, 487-496



Perko et al hypothesized there is parasympathetic contribution to mesenteric vasorelaxation during HUT.

8 healthy asymptomatic adults without OI Measurements: SMA diameter, SMA flow, resistance

Blood flow (unchanged) = <u>Blood pressure (decreased)</u> Vascular resistance (decreased)



Response to HUT with Cholingeric Blockade

Cholinergic blockade

Measurements: SMA diameter, SMA flow, resistance

Blood flow (decreased by 39-42%) = <u>Blood pressure (decreased)</u> Vascular resistance (increased)

This supports that there is a cholinergic contribution to the mesenteric artery vasorelaxing response to the central hypovolemia induced by HUT.



Physiological Changes with Head Up Tilt





Beta blockers (BB) have successfully been used in adults for OI.

The exact mechanism is not clear







Through this study, we want to evaluate the variation of SMA flow and resistance in pediatric patients with OI and GI complaints during HUT.

We also want to assess whether the variation in SMA flow can be predictive of treatment response to BB therapy in these patients.



Reviewed charts of children (ages 8-19) who underwent HUT from March 2011 to January 2016.

Included cases with abdominal complaints

These patients also had simultaneous SMA flow analysis.

 Fujimura et al (1998) developed a non-invasive, simple and reproducible method to detect changes in mesenteric blood flow after physiologic stimuli.



Ultrasound parameters recorded included:

- the diameter of the SMA
- SMA time average mean velocity (TAV)

SMA blood flow (mL/min) = TAV x area of the vessel x 60

Vascular resistance = <u>Mean Arterial Pressure</u> SMA blood flow



Significant test:

A reduction in SMA flow greater than 50% and/or An increase in resistance greater than 100%

We also collected data of response to treatment.

- Reviewing charts or calling the patients directly



Results: Patient Demographics and Complaints

14 patients – HUT + abdominal complaints

- 10 patients with SMA flow analysis
- 4 patients did not have SMA flow analysis due to air in the abdomen



S. No	Sex	Age	Year	Abdominal Complaint	Syncope or Dizziness	Migraine	SMA study
P1	F	18	2011	х	x		Yes
P2	М	16	2011	x	x		Yes
P3	М	14	2012	x	x		Yes
P4	F	19	2012	x	x	x	Yes
P5	F	17	2012	х	x		Yes
P6	F	18	2013	х	x		No
P7	F	17	2013	х	x	x	No
P8	F	15	2014	х			Yes
P9	F	15	2014	х	x	x	Yes
P10	F	12	2015	х			Yes
P11	F	15	2015	х			Yes
P12	F	8	2015	х	X	x	Yes
P13	F	19	2016	х	х		No
P14	F	15	2016	х	X	х	No



Results of the HUT and SMA Flow Study

S. No	Abdominal Complaint	Dizziness & syncope	Migraine	Tilt test results	Result of SMA test
P1	x	x		Positive	Positive
P2	х	x		Positive	Positive
P3	x	x		Positive	Positive
P4	х	x	x	Positive	Positive
P5	х	x		Positive	Positive
P6	x	x		Negative (72)	N/A
P7	x	x	x	Positive	N/A
P8	x			Positive	Positive
P9	x	x	x	Positive	Positive
P10	x			Negative (62)	Positive
P11	x			Negative (94)	Negative
P12	x	x	x	Positive	Positive
P13	х	x		Positive	N/A
P14	Х	Х	х	Positive	N/A







Results: SMA Flow studies

S.N	Tilt test results	SMA Diameter Baseline	SMA TAV - Baseline	SMA Blood Flow	Baseline - Resistance	Lowest SMA flow (HUT)	% Reduction SMA flow	Resistance change	Result of SMA test
P1	Positive	0.5	19.1	0.9	72.3	0.239749	73%	272%	Positive
P2	Positive	0.68	30.5	2.667	29.369	1.07	60%	141%	Positive
P3	Positive	0.54	42.5	5.84	12.5	3.31	43%	188%	Positive
P4	Positive	0.7	41	3.79	17.98	1.27	66%	241%	Positive
P5	Positive	0.5	75	3.54	19.83	1.02	71%	337%	Positive
P6	Negative								N/A
P7	Positive								N/A
P8	Positive	0.5	38	1.79	65.3	0.442	75%	161%	Positive
P9	Positive	0.5	49	2.32	35	1.18	49%	489%	Positive
P10	Negative	0.5	25	1.18	60.63266	0.586	50%	124%	Positive
P11	Negative	0.55	20	1.14	65.259	0.772	32%	18%	Negative
P12	Positive	0.33	33	0.679	103.49	0.253	63%	177%	Positive
P13	Positive								N/A
P14	Positive								N/A



Results: Post-Treatment

S. No	Tilt test results	Result of SMA test	Treatment	Results
P1	Positive	Positive	Amitryptiline	None
P2	Positive	Positive	Amitryptiline	None
P3	Positive	Positive	Amitryptiline	Unknown
P4	Positive	Positive	Propranolol	Improved
P5	Positive	Positive	Propranolol ***	Improved
P6	Negative	N/A	on propranolol prior to HUT	Improved
P7	Positive	N/A	Amitryptiline	Unknown
P8	Positive	Positive	Propranolol + Amitryptiline	Improved
P9	Positive	Positive	Metroprolol	Improved
P10	Negative	Positive	Hydration	Improved
P11	Negative	Negative	Hydration	Unknown
P12	Positive	Positive	Hydration	Improved
P13	Positive	N/A	Hydration	Unknown
P14	Positive	N/A	Fludrocortisone + Amitryptiline	Improved



Indian Hydration in Greece







All patients with GI symptoms and OI had a positive SMA flow analysis.

One patient with only abdominal complaints with change in position had negative SMA flow analysis.

We started using BB therapy in 2012 on patients with positive SMA flow analysis.





All patients who were started on BB therapy showed improvement in symptoms.

Half of the patients received amitriptyline (AMI) alone (before 2012) or in combination with another medication.

There was no improvement seen in patients receiving amitriptyline alone.





Pediatric patients with OI and GI symptoms often have an exaggerated response to HUT which may be represented as significant reduction in SMA flow and/or increase in SMA resistance.

BB therapy might be useful in alleviating the symptoms in these patients.





Small sample size

BB blocker effectiveness is reported by patients – subjective

- we are unable to perform a repeat post tilt test for objective data for ethical reasons

We do not have a control group of patients who have a positive HUT and negative SMA study per our criteria.

We do not know the response of BB therapy in this group.



Thank you!





Results





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 While central hypovolemia during HUT evokes a reduction in SMA resistance resulting in maintenance of regional flow, patient who were given cholinergic blockade demonstrated reductions in SMA flow by 39-42% and increase in mesenteric artery resistance reflected in reduction in the diastolic blood velocity by 41-56%.



 Autonomic dysfunction caused a reduction in SMA mean blood velocity by 39-42% corresponding to volume flow reductions by 35 and 41%. There is also an increase in mesenteric artery resistance in patient with autonomic dysfunction.



- Fujimura et al developed a non-invasive, simple and reproducible method in detecting changes in mesenteric blood flow after physiologic stimuli.
- Impaired adrenergic vasomotor function plays a key role in the mechanism of orthostatic and post-prandial hypotension in patients with autonomic failure.

c circulation can play a role in overall

• Splanchnic organs receive about 25% of the cardiac output at rest and contain 30% of the total blood pool.



Ohm's Law

 $V = I \times R$

- I is the current through a conductor
- V is the voltage measured across the conduct
- R is the resistance of the conductor



Review

 HUT reduces cardiac stroke volume and induces hypotension when maintained for ~30 minutes.

Simultaneously, SMA resistance decreases, but its blood flow is maintained.

• I = V/R or Flow = Blood pressure/Resistance



