Immunology of arterial hypertension – immunological phenomena in children with primary hypertension

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Immunology of arterial hypertension

**INNATE IMMUNE SYSTEM**

- responsible for fast and non-specific immediate inflammatory response
- recruited to eliminate infection or in response to tissue injury
- consists of cells (granulocytes, monocytes, macrophages, dendritic cells, mast cells, NK lymphocytes)

**ADAPTIVE IMMUNE SYSTEM**

- specific response of T and B cells respond to exo- or endogenous antigens

- soluble factors (interferons, acute phase proteins, cytokines, chemokines, defensins, complement)
Immunology of arterial hypertension

The cells of innate immune system: granulocytes, monocytes, dendritic cells – express pattern recognition receptors (PRRs) which recognize pathogen associated molecular patterns (PAMPs) that are expressed and shared by large groups of pathogens or damage associated molecular patterns (DAMPS) that represent structures of damaged cells. The cell of adaptive immune system: lymphocyte
Immunology of arterial hypertension – back to the past

**ROLE OF T CELLS**

Immunosuppression (6-MP, cortisone) lowers blood pressure in rats that had partial renal infarction. *White & Grollman 1964*

Transfer of lymphocytes from rats with unilateral renal infarction caused hypertension in recipient rats. *Okuda & Grollman 1967*

Cellular infiltrates in arteriolar walls and periadventitial space in humans with different forms of arterial hypertension (PHAEO, PA, PH, RVH). *Olsen 1972*

**ROLE OF THYMUS**

Intact thymus is necessary for maintaining of HT in mice with RVH. *Svendsen UG 1975*

**Hypothesis:** HT induces thymus-dependent immune reactions against substances derived from the vascular walls. The early phase of HT which follows partial infarction of the kidney and contralateral nephrectomy is thymus independent. *Svendsen UG 1976*
Immunology of arterial hypertension

Cellular infiltrates in arteriolar walls and periadventitial space in humans with different forms of arterial hypertension (PHAEO, PA, PH, RVH). *Olsen 1972*

**EXPERIMENTAL STUDIES ON THE ROLE OF IMMUNE SYSTEM IN HT (SELECTED)**

<table>
<thead>
<tr>
<th>IS lowers BP in renal infarction (rats)</th>
<th>White &amp; Grollman 1964</th>
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<tbody>
<tr>
<td>Thymectomy/splenectomy prevents HT in partial renal infarction</td>
<td>Okuda &amp; Grollman 1967</td>
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<tr>
<td>Intact thymus necessary for maintaining of HT (renal infarction; mice)</td>
<td>Svendsen 1975/76</td>
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<tr>
<td>Reduction of BP in SHR by ATG</td>
<td>Takeichi et al. 1981</td>
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<td>HT not maintained in athymic nude mice; thymus grafts from haired mice caused sustained HT (DOCA-salt rats)</td>
<td>Svendsen 1976</td>
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<td>AT2 does not elevate BP in RAG-/-mice. T-cells restored HT</td>
<td>Guzik et al. 2007</td>
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<tr>
<td>T-reg lowered BP and TOD in mice infused with AT2/ALDO</td>
<td>Barhoumi et al. 2011</td>
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**HUMAN STUDIES - ADULTS**

| IL10 polymorphism associates with HT in adult Tatars | Timasheva et al. 2008 |
| Adults with PH had more lymphocytes with markers of aging CD57+/CD8+ and CD28-/CD8+ vs normotensive controls | Youn et al. 2013 |
| Increased number of activated T cells bearing the memory phenotype (CD3+/CD45RO+) both in the humanized mouse model, and in adults with PH | Itani et al. 2016 |
| B-cell activating factor in hypertensive pregnant women | Stohl et al. 2017 |
Immunology of arterial hypertension – clinical evidence. Adults.

NHANES III – hypertensive subjects had higher numbers of PBL than normotensives *Park CS et al. Kor Circ J* 2007

HIV infected pts have lower BP *Palacios R et al. HIV Med.* 2006

MMF lowers BP after RTx *Morales JM Kidney Int Suppl.* 2002

HT is associated with elevation of pro-inflammatory cytokines (IL17, IL6, TNFa, IFNy) and decrease of anti-inflammatory cytokines (IL10)

*Li YY PLoS One 2012*
Metabolic abnormalities
Oxidative stress
SNS activation

Neoantigens
T cells

Childhood
Metabolic abnormalities
Oxidative stress
SNS activation

Adolescence

Adulthood

Harrison DG et al. Hypertension 2011; 57: 132 - 40
What does an adolescent with primary hypertension look like? Intermediary phenotype of PH.

- Adolescents with PH have increased ratio of fat mass to lean body mass.
  
  *Pludowski P et al. Hypertension 2008*

- Hypertensive children are taller and have a greater BMI than normotensive peers.
  

  PH in childhood is associated with more advanced biological maturity expressed as difference between bone age (BA) and chronological age (CA) than in BMI-matched normotensive children
  
  *Pludowski P et al. Hypertension 2009*

- Metabolic syndrome is 10 times more prevalent among hypertensive adolescents than in general pediatric population
  
  *Litwin M et al. Am J Hypertens 2007*
The gain of weight and the BP elevation may be the intermediate phenotypes of an underlying overactivity of sympathetic system.

**Figure 1.** Risk of subsequent obesity according to BP status. Subjects were weight matched at baseline and followed for 10 years. NBP indicates normal blood pressure; B-HBP, borderline high blood pressure; HBP, high blood pressure. *P<0.05 for trend. Adapted from Kannel et al.9

Elevation of BP and faster HR may precede obesity and metabolic abnormalities.
Adolescents with primary hypertension have disturbed blood pressure and heart rate rhythmicity – significantly increased prevalence of 12-hour rhythms and delayed acrophases (time from midnight to highest value of BP during rhythm – marker of persistence of sympathetic activity).

Litwin M et al. Pediatr Res 2010
Immunology of arterial hypertension – evidence from pediatric studies

- Intermediate phenotype of hypertensive child
- Metabolic abnormalities
- SNS activation
- Immune activation
  - innate immunity
  - adaptive immunity
- Do we have targeted treatment?
Immune activation in children with primary hypertension — association with metabolic abnormalities and visceral obesity. Innate immunity - focus on cytokines and chemokines.

Increased serum concentrations of MIP-1β and RANTES in hypertensive children in comparison with normotensive controls

The greater number of metabolic abnormalities, the greater immune activity.

The greater immune activity (low adiponectine), the greater cIMT.

Litwin M et al. Pediatr Nephrol 2010
Immunology of hypertension. Pediatric studies. Innate immunity. Focus on peripheral blood leucocytes.

- PBL express genes and secrete metalloproteinases (MMPs) and their inhibitors (TIMPs)
- PBL possess full genetic machinery of renin-angiotensin system:
  - genes of ACE, AGT, renin, ATII receptor (AT2R1)
  - and of adipocytokines:
    - leptin, adiponectin receptor (ADIPOR1)
- PBL express receptors of sympathetic and parasympathetic nervous system: Achα7R, β1R, β2R and 1 α1R,
Immunology of hypertension. Pediatric studies. Innate immunity. Focus on peripheral blood leucocytes.

TIMP1 vs aortic PP: $r = 0.367; p < 0.05$
AugPress: $r = 0.428; p < 0.05$
AugInd: $r = 0.404; p < 0.05$


Correlation analysis between MMP14 expression and left ventricular mass index (LVMI). (Spearman correlation analysis $p = 0.002; r = 0.324$)
LVMI = 31.6591 + 0.8422$x$

Trojanek J et al. Hypertension, submitted
Immunology of hypertension. Pediatric studies. Innate immunity. Focus on peripheral blood leucocytes.

PBL possess full genetic machinery of renin-angiotensin system and of adipocytokines. 6-month of nonpharmacological treatment led to significant decrease of REN, ACE and Adipor1 genes expression.

However, pattern of gene expression was still different from normotensive children.
Adolescents with PH form a heterogenous group: those who have low serum adiponectin and high expression of AdipoR - have more severe hypertension and signs of hypertensive arterial remodelling (increased cIMT)

Immunology of hypertension. Pediatric studies. Adaptive immunity. Focus on lymphocytes

Controls – 35; mean age - 15 yrs
Hypertensive children – 32; mean age 15 yrs

Loss of CD31 molecule on CD4 and CD8 lymphocytes

Loss of CD31 molecule on naive memory CD4 and CD8 lymphocytes
Subclinical arterial injury and left ventricular hypertrophy in adolescents with PH is associated with declined thymic function and increased pool of T cells bearing effector/memory phenotype (loss of CD31 receptor).
Immunology of hypertension. Focus on interaction between innate and adaptive immunity. T-reg, TH17 lymphocytes and adipokines.

Tregs number is greater (1.9 times) in hypertensive children than in normotensive controls.

Hypertensive children have greater number of Th17 and IFN and TNF producing lymphocytes.

The greater expression of ADIPOR1 - the lower serum adiponectin, the greater cIMT, the higher BP.

β2R expression and IF correlated with AoBP, PWV and cIMT, and extracellular expression of α1R correlated with LVMi, AoBP and SV (all p<0.05). Hypertensive children had increased expression of α1 but not β2 receptors on PBN. Increased expression of α1 receptors correlated with PWV, LVMi, cIMT and central BP. These findings indicate on involvement and cooperation of autonomic nervous system and immune system in children with primary hypertension.

Niemir ska A et al. Valencia, ICHCA 2018
Immunology of hypertension. Is there any evidence of change in immune activation caused by antihypertensive treatment? Pediatric experience.

When to initiate antihypertensive treatment. One or more of the conditions listed in the box need to the start of antihypertensive drugs. Persistent hypertension, despite nonpharmacological measures, needs to start antihypertensive drug treatment.

Lurbe E et al.: ESH guidelines J Hypertens 2016
Modulation of expression of genes involved in inflammatory reactions during antihypertensive treatment – adults with primary hypertension. Peripheral blood leucocytes – innate immunity

Antihypertensive treatment led to decreased expression of genes of receptors of
- IL-4,
- IL-10A,
- IL-13α1,
- IL-1
- IL-1AP
But mainly in males.

Chon H et al. Hypertension 2004
Immunology of hypertension – effects of treatment on immune activation. Pediatric data.

Pediatric hypertension trials mainly concern BP decrease. Only few analyzed effects of treatment on TOD. Chaturvedi S et al. Evid Base Child Health 2014

**EFFECT ON TOD**

Ramipril – decrease of LVM. N = 21.
Seemann T et al. Am J Hypertens 2007

LVH regression in children with PH treated with enalapril. N = 22.
Kupferman JC et al. Pediatr Nephrol 2010

Decrease of LVMi and cIMT after 1 year of treatment. N = 50

Regression of LVMi, LVH, cIMT and metabolic abnormalities after 1 year of antihypertensive treatment. N = 86
Litwin M et al. Pediatr Nephrol 2010

**EFFECT ON METABOLIC AND IMMUNE ABNORMALITIES**

Oxidative stress reduction after 12 mts treatment. N = 86

Normalization of metabolic abnormalities and inflammatory activity after 12 mts treatment.
N = 86.
Litwin et al. Pediatr Nephrol 2010

Change in MMPs/TIMPs expression after 6 mts non-pharmacological treatment. N = 23
Litwin M et al. Hypertension 2013

Effects of 12 mts antihypertensive treatment on ANS activity. N = 50.
Niemirska A et al. Hypertension 2013

Candesartan led to decrease of microalbuminuria. N = 19 of 93
Schaeffer F et al. J Hypertens 2010
Antihypertensive treatment modulates genes expression in blood leucocytes of hypertensive children.

PBL possess full genetic machinery of renin-angiotensin system and of adipocytokines. 6-month of nonpharmacological treatment led to significant decrease of REN, ACE and Adipor1 genes expression.

However, pattern of gene expression was still different from normotensive children.
Relation between decrease of inflammatory activity and target organ damage regression in children with primary hypertension

N = 86 (22 girls); 14.1 ±2.4 yrs

12 mts treatment based on life-style intervention and ACEi/ARB

24hABPM

Left ventricular mass & carotid IMT

Metabolic abnormalities

Immune activity

Litwin M et al. Pediatr Nephrol 2010
Normalization of BP in 70% of pts
Disappearance of severe left ventricular hypertrophy
Significant decrease of carotid intima-madia thickness
Decrease of prevalence of metabolic syndrome by 50%
Normalization of elevated hsCRP

However, the only predictors of regression of target organ damage was not blood pressure decrease but decrease of visceral fat expressed as decrease of waist circumference and **normalization of inflammatory markers**.

Step-wise regression analysis revealed that the main predictor of an LVMi decrease was a decrease in abdominal fat expressed as a decrease in WC ($\beta = 0.558$), explaining about 28% of variability ($R^2 = 0.280$, $p = 0.005$), for WCsA-SDS a decrease in WC ($R^2 = 0.332$, $\beta = 0.611$, $p = 0.009$), and for the cIMT-SDS decrease the main predictor was a decrease in hsCRP concentrations ($R^2 = 0.137$, $\beta = 0.412$, $p = 0.03$).
Significant decrease of oxidative stress after 12 mts of treatment

Oxidative stress markers (ADMA, oxyLDL) correlated with hsCRP.

Normalization of inflammatory markers and regression of TOD was associated with significant decrease of oxidative stress.

p < 0.0001
Immunology of childhood hypertension.
Conclusions.

- There is strong evidence that immune system, both innate and adaptive, plays role in pathogenesis of PH.
- The few pediatric studies showed that PH in children and adolescents involves both innate and adaptive immune systems. There is evidence that childhood PH is associated:
  - with inflammatory activity,
  - altered expression of genes involved in inflammatory reactions,
  - disturbed distribution of T cell subpopulations,
  - accelerated maturation of T cells and relation between autonomic nervous system and immune cells.
- Both non-pharmacological and pharmacological antihypertensive treatment led to
  - decrease of inflammatory activity,
  - changes of genes expression pattern and TOD regression,
  - TOD regression was significantly associated with decrease of inflammatory activity and SOX.
Childhood hypertension as an neuro-immuno-metabolic disease

Metabolic abnormalities and metabolic load

Autonomic Nervous System activation

Oxidative stress

Adipocyte dysfunction

Innate and adaptive immunity
Immunology of primary hypertension in children and adolescents - challenges

What is the first?

Primary defect of innate immunity or of lymphocyte?

or

Secondary to neuro-metabolic abnormalities?

Is it reversible?

Is there drug specific effect?

Is there point of no return?

Etc....
What do you think was first? The chicken or the egg?

I think the chicken was first

I think the egg was first

WHO CARES?? THEY ARE BOTH TASTY!!!
The mosaic theory of hypertension

By

I. H. Page

Focal points 1960:

Elasticity
Neural
Chemical
Reactivity
Volume
Vascular caliber
Viscosity
Cardiac output
Immunology of arterial hypertension

The mosaic theory of hypertension

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Focal points 1960:

- Elasticity
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- Vascular caliber
- Viscosity
- Cardiac output

The Mosaic Theory 32 Years Later

By

Irvine H. Page, M.D.

Hypertension 1982

Focal points 1982:

“while the principles are unchanged, the focal points now may be more appropriately expressed as:”

- Genetic
- Environmental
- Anatomical
- Adaptive
- Neural
- Humoral
- Hemodynamic
Immunology of arterial hypertension – back to the future

The Mosaic Theory revisited: common molecular mechanisms coordinating diverse organ and cellular events in hypertension

David G. Harrison

Genetic variations influence pro-oxidant and antioxidant enzyme function and expression

Environmental influences disorder

Polymorphisms in cytokine genes (IL-6, TNFα, IL-23, others) associate with hypertension

Environmental pollutants activate macrophages and T cells. Nutrient excess is proinflammatory. Emotional stress promotes hypertension via T cell activation

Hypertension induces inflammation at specific anatomic sites - renal cortex, hypothalamus, perivascular adipose tissue

Inflammation modulates adaptive responses to hypertension, including vascular hypertrophy and stiffening

Hypothalamic inflammation increases sympathetic outflow. Immune cells possess adrenergic and cholinergic receptors. Lesions in the AV3V region prevent T cell activation in hypertension