Hemodynamic abnormality that initiates salt-induced hypertension in rat model of primary aldosteronism

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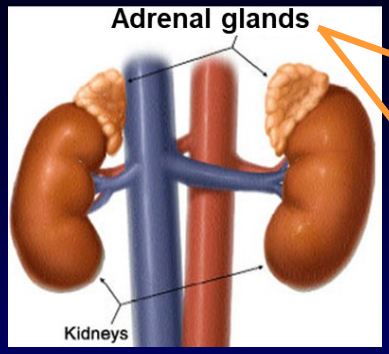
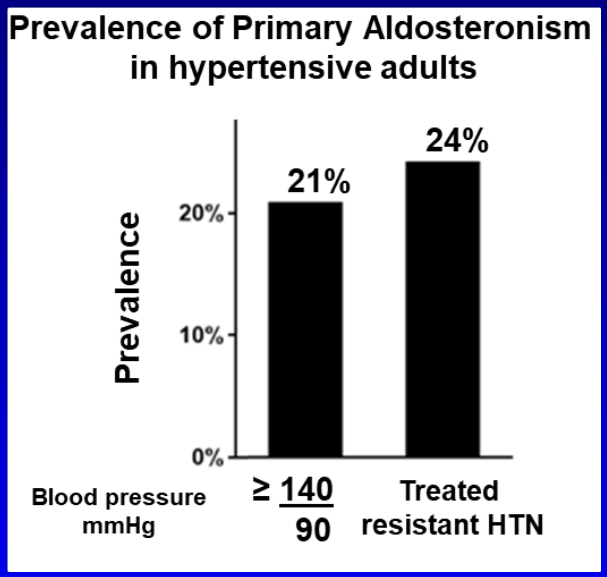
Primary aldosteronism is a well-known cause of salt sensitivity and salt-dependent hypertension



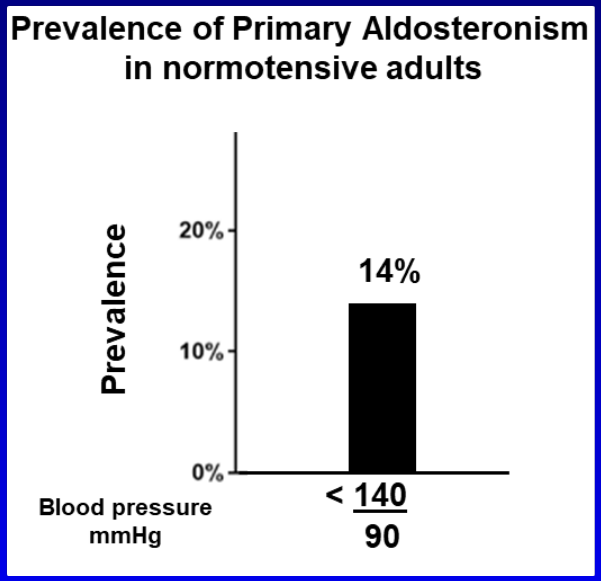
Aldosterone + High NaCl diet → Increased blood pressure

Aldosterone + Low NaCl diet → No change in blood pressure

Primary aldosteronism may be present in 20-25% of hypertensives and 10-15% of normotensives. It could contribute to nearly 50% of cases of salt sensitivity.



The Unrecognized Prevalence of Primary Aldosteronism
Brown JM et al. Annals of Internal Medicine. 2020

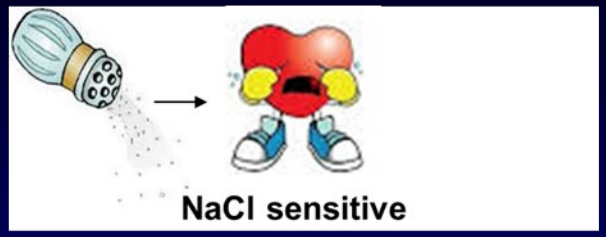


Continuum of Renin-Independent Aldosteronism in Normotension Baudrand R et al. Hypertension 2017

How Does Aldosterone Promote Salt-Dependent Hypertension ?

The traditional "volume-loading" theory of Guyton and colleagues

Hyperaldosteronism



↑ Aldosterone → ↑ ENaC activity in renal tubules

↓ Increases renal salt reabsorption

↓ Retain large amounts of salt and water

↓ Increases blood volume

↓ Increases cardiac output

↓ Initiate the hypertension

Normal aldosterone

Suppress aldosterone levels

↓ Rapidly excrete salt

↓ Retain little or no salt and water

↓ Little or no increase in blood volume

↓ Little or no increase in cardiac output

↓ Little or no increase in blood pressure

Problem

Theory is based on studies that did not include salt loading in controls with normal aldosterone levels to those with hyperaldosteronism with respect to salt induced changes in CO and SVR

A controlled study of the hemodynamic effects of salt-loading in an animal model of primary aldosteronism

Continuous 24-hr hemodynamic monitoring

Mean Arterial Pressure, Cardiac Output, Heart Rate, Systemic Vascular Resistance

Rat model of Primary Aldosteronism

SD rats with unilateral nephrectomy

Continuous infusion of aldosterone

Low NaCl Diet (0.26 % NaCl)

High NaCl Diet (4.0 % NaCl)

Continuous infusion of vehicle solution

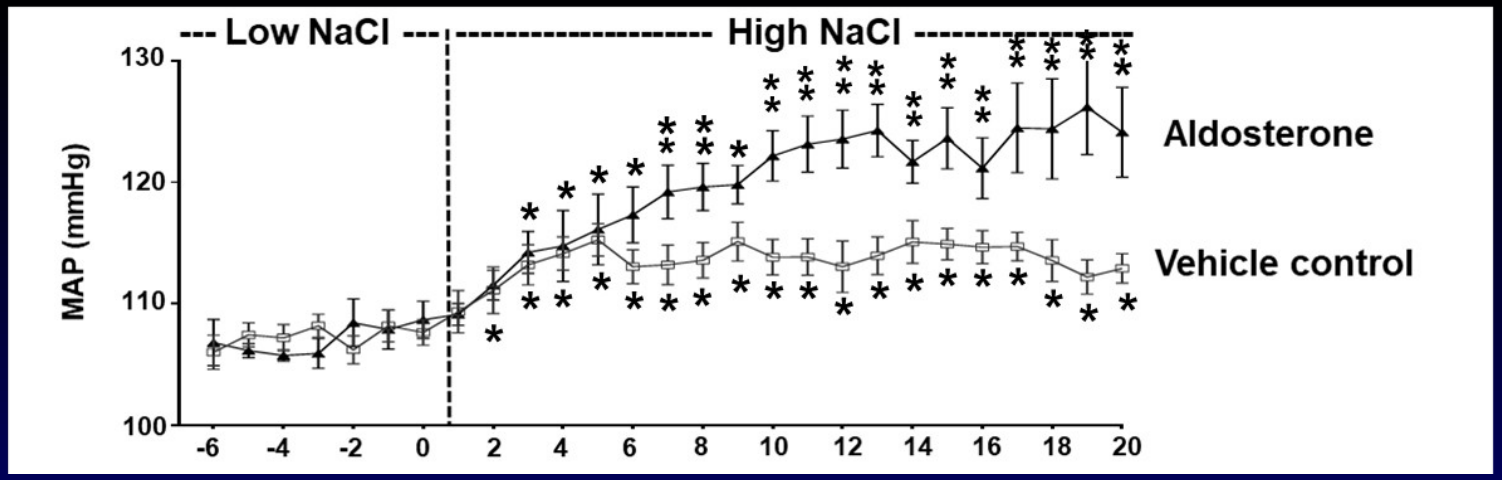
Doppler flow probe around the aorta to measure CO

Telemetry probe in carotid artery to measure BP

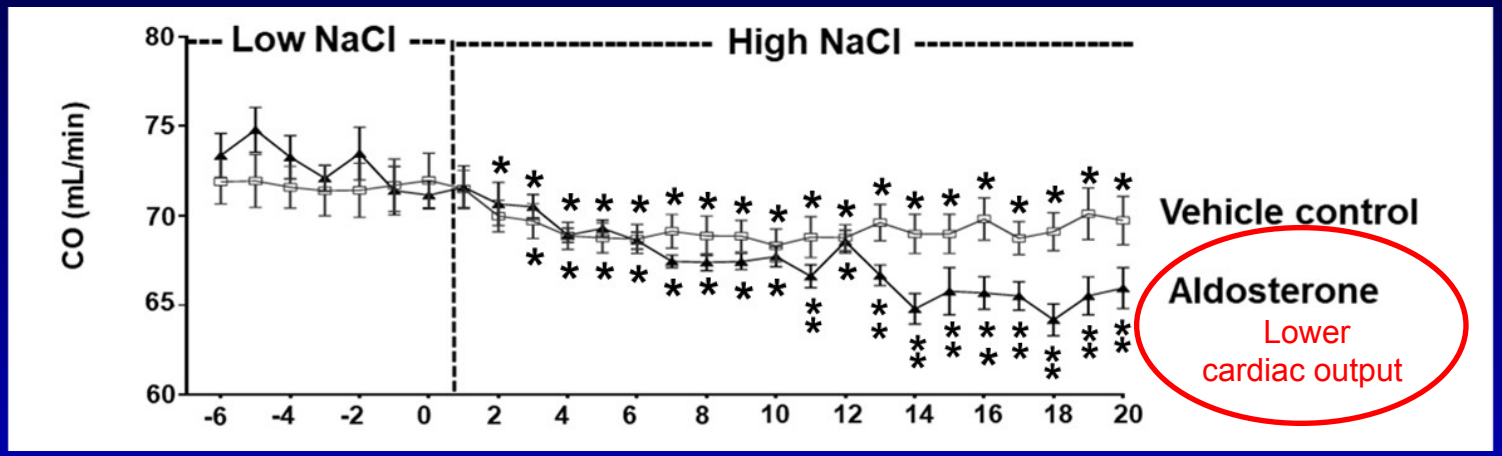
Test the claim of Guyton, Hall, and others that:

"In hyperaldosteronism, the salt-dependent hypertension is caused by a primary increase in cardiac output followed by a secondary vasoconstriction"

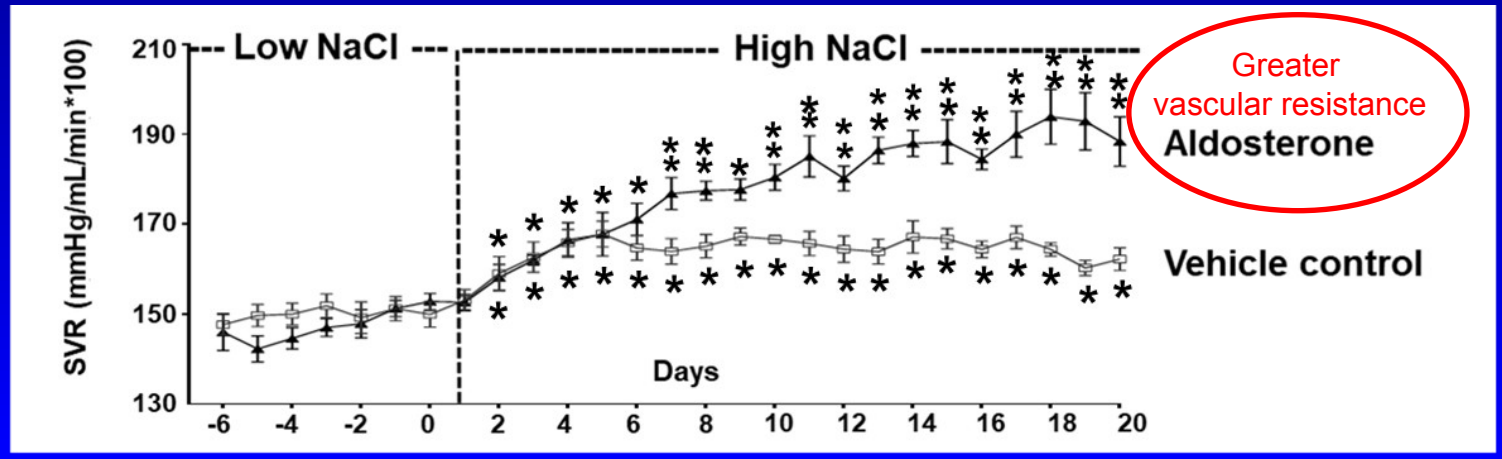
Mean arterial pressure
(24 hour averages)



Cardiac output
(24 hour averages)

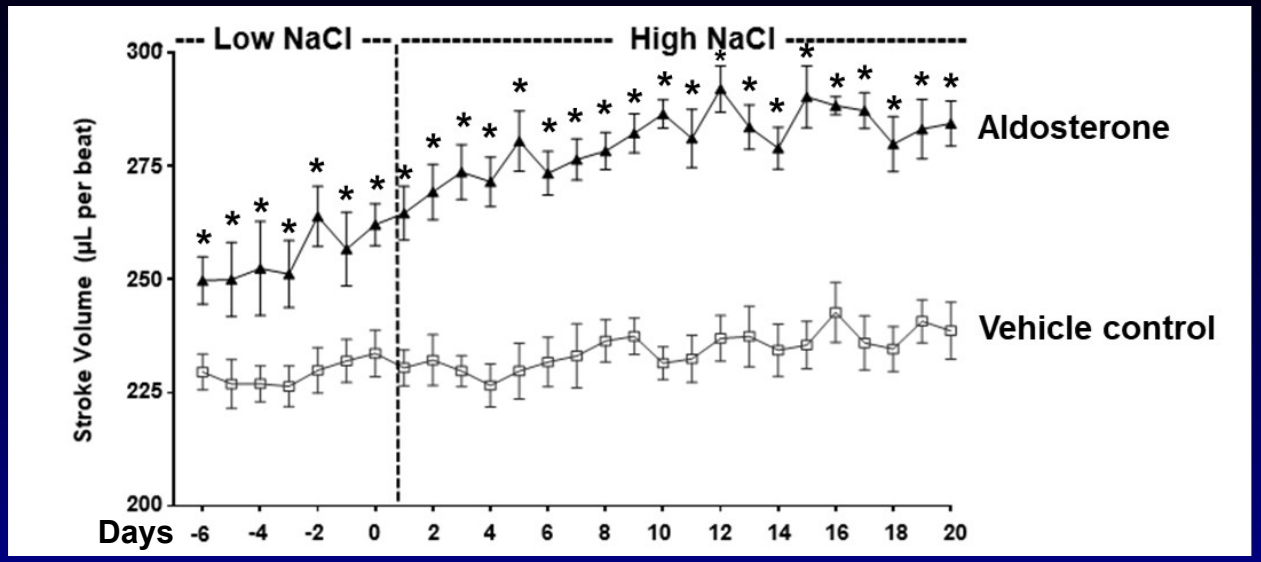


Systemic vascular resistance
(24 hour averages)

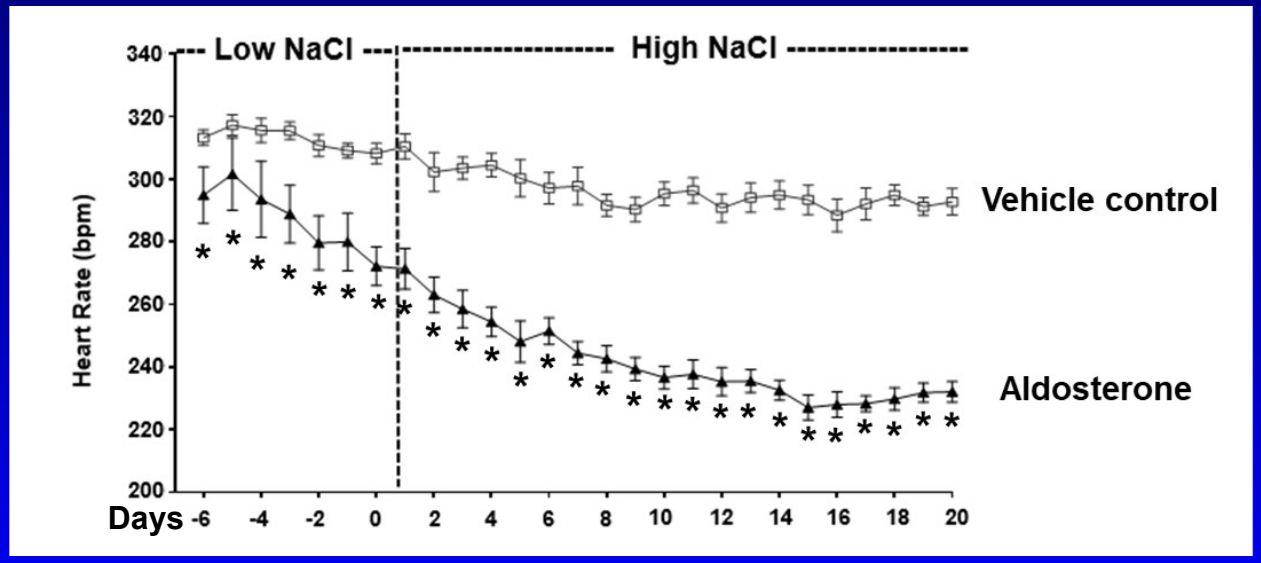


In hyperaldosteronism, what causes cardiac output to decrease during initiation of salt-induced increases in blood pressure?

Stroke volume
(24 hour averages)



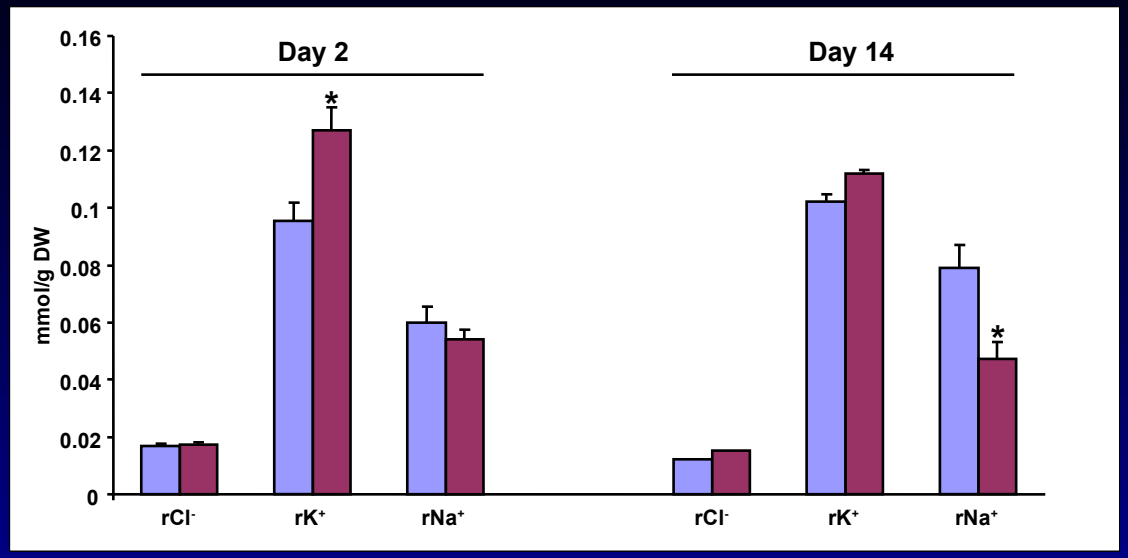
Heart rate
(24 hour averages)



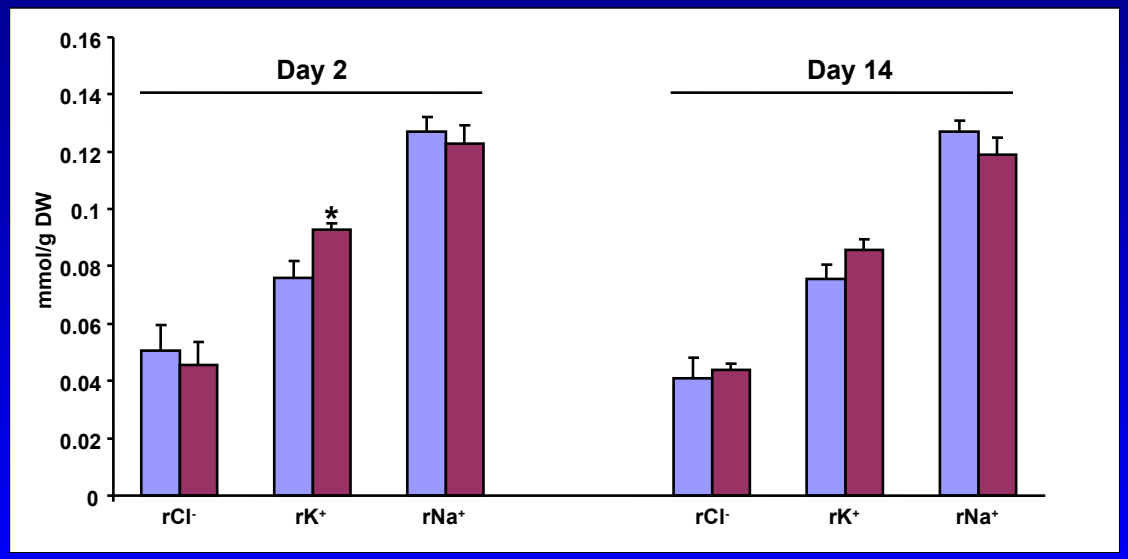
CO decreased presumably as a consequence of increases in SVR, decreases in heart rate, and potentially increases in afterload.

Tissue electrolytes during initiation of salt-sensitive hypertension

Carcass

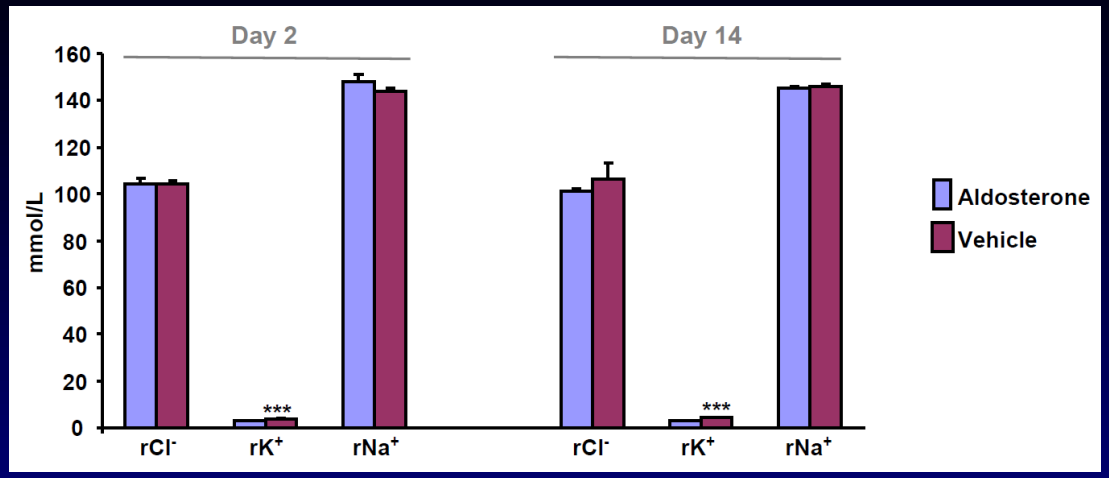


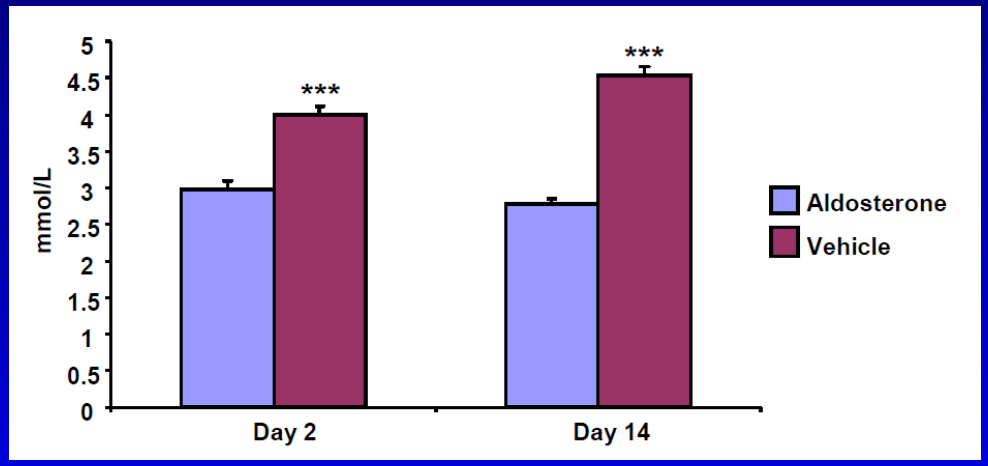
Skin



Aldosterone
Vehicle

Plasma electrolytes during initiation of salt-sensitive hypertension

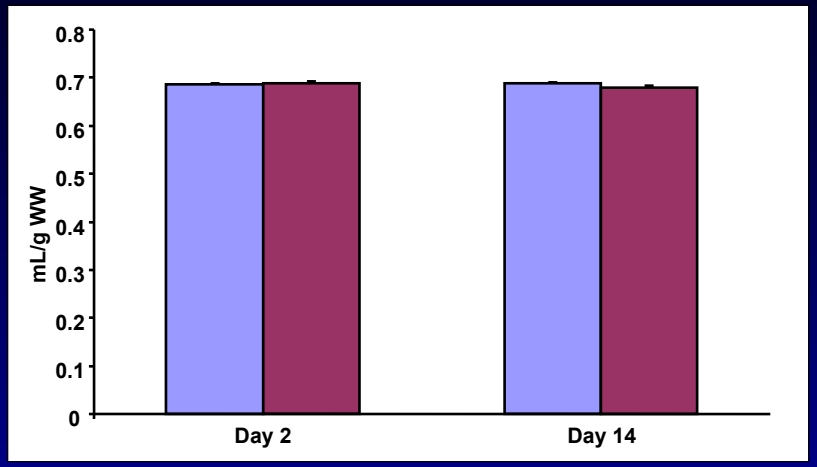




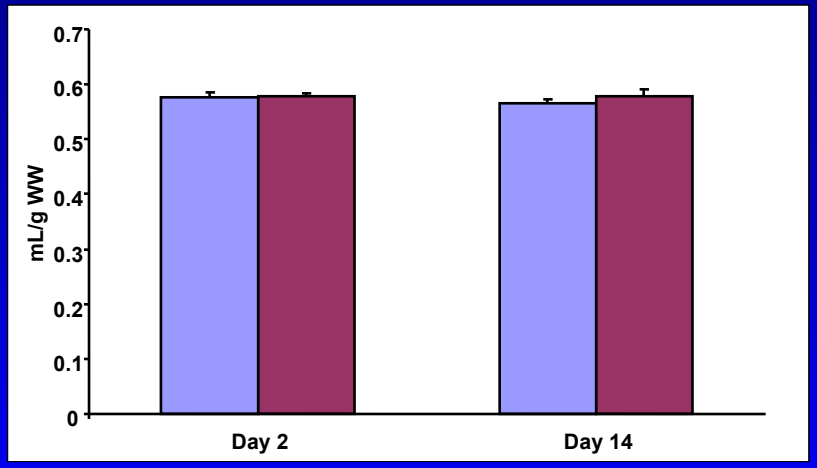
Plasma potassium has a vasodilator function by stimulation of membrane Na^+, K^+-adenosine triphosphatase activity, resulting in hyper-polarisation and relaxation of the vascular smooth muscle cells. Plasma potassium is also involved in nitric oxide production.

Tissue water content during initiation of salt-sensitive hypertension

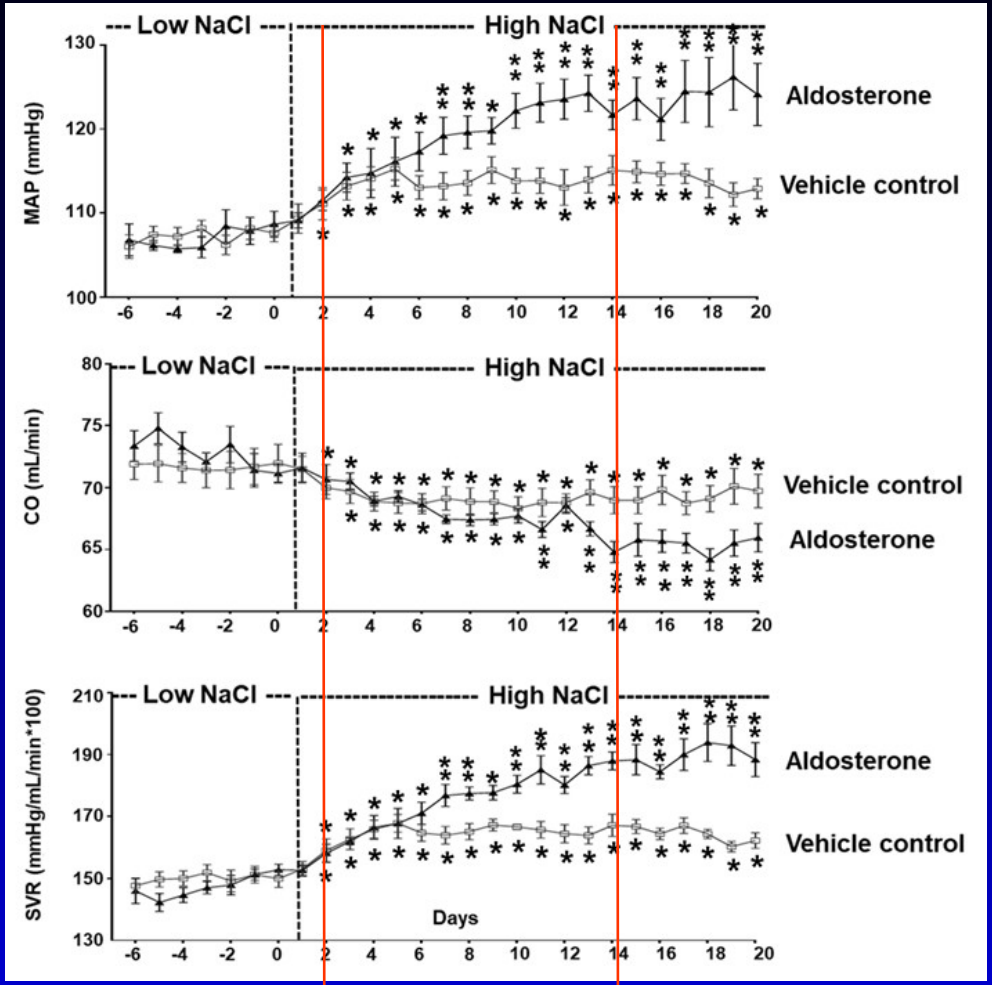
Carcass



Skin



Aldosterone-induced hypokalemia precedes initiation of salt-induced hypertension without water and sodium retention



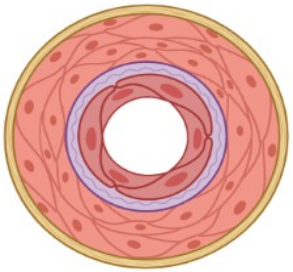
- Hypokalemia prior hypertension initiation after salt loading
- No retention of salt and water
- Expression of genes from BP hyperosmotic response in the skin
- Osmotically inactive Na^+ accumulation in tissues after hypertension initiation
- Expression of genes from BP muscle development and contraction (vascular response) in the skin

The traditional "volume-loading" theory of Guyton and colleagues

In hyperaldosteronism, the salt-dependent hypertension is caused by a
"a primary increase in cardiac output followed by a secondary vasoconstriction"

"Vasconstriction" Theory

In hyperaldosteronism, the salt-dependent hypertension is initiated
by primary increases in systemic vascular resistance - not increases in cardiac output



Vasoconstriction

Increase dietary intake of NaCl
+
Primary aldosteronism
↓
↑ Vascular resistance + ↓ Cardiac output
↓
Initiation of hypertension

Fall in cardiac output

Summary and Conclusion

- In primary aldosteronism, salt-dependent hypertension can be initiated by primary increases in systemic vascular resistance
- Contrary to the traditional “volume-loading” theory, increases in Na^+- driven body water overload followed by increased cardiac output are not necessary for initiation of salt-dependent hypertension in hyperaldosteronism
- Increases in systemic vascular resistance can initiate the salt-dependent hypertension despite the occurrence of simultaneous decreases in cardiac output
- Aldosterone-induced hypokalemia may cause primary abnormal vascular resistance responses to salt by altering the balance in activity between vasoconstrictor and vasodilator pathways
- It can be concluded that in primary aldosteronism, the hemodynamic mechanism of hypertension initiation is better explained by the vasoconstriction theory than the traditional “volume-loading” theory

Kurtz TW. Morris RC Jr. Pravenec M. Lujan HL. DiCarlo SE. Hypertension in Primary Aldosteronism Is Initiated by Salt-Induced Increases in Vascular Resistance With Reductions in Cardiac Output. *Hypertension* 80:1077-1091. 2023