# A BIOMATHEMATICAL EQUATION FOR HEMODYNAMIC PRESSURE ALTERATION AND CARDIAC ARTERIAL ELASTIN EXPRESSION

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## ABSTRACT (186/250)

The hypothesis of studies is that acetyl salicylic acid (Aspirin, ASA) treatment can induce elastin gene. An increased lysine (K) residue would act as a source for NAD+ dependent histone deacetylase protein as it can deacetylate elastin at multiple lysine sites in cultured HL1 cardiomyocytes. A mathematical equation deduce the hemodynamic pressure state in normal and artherosclerotic model. Atrial Cardiomyocyts HL1 cells were cultured in Claycomb medium with 10% FBS, 100μmol/L norepinephrine and 4mmol/L L-glutamine (Invitrogen, Carlsbad, CA) in gelatin coated flasks. Cells were maintained at 37°C in an atmosphere containing 5% $CO_2$. Cells were then incubated with either, 50 μM and 0.25 mM ASA for 48 h in the same medium. Respective controls were maintained with alcohol alone. At the end of the treatment, the medium was removed and the cells were washed with PBS and harvested in Trizol® for isolation of RNA. RT-PCR was performed for the analysis of gene expression. Our results in cultured HL1 cardiomyocytes showed ASA treatment induced elastin gene. We conclude from our results that ASA can increase elastin gene suggests that it can improve vascular stiffening and normalize hemodynamic pressure.

**KEYWORDS:** Acetyl Salicylic acid, Elastin, Lysine.

## INTRODUCTION

In normal cardiac tissue arteries have very important role, it can adapt to the changes in hemodynamic condition. Atherosclerosis is characterized by narrowing of arterial lumen which is also called as stenosis and is main cause of coronary artery disease (CAD).[1] The change in hemodynamic condition causes abnormal biological milique with a change in the

turbulence and reduction in blood flow. The entire process of atherosclerosis begins with disruption of endothelial function due to the accumulation of lipoprotein droplets in the intima of the coronary vessels. These disturbances occurs due to change in arterial wall lining.[2,3]

The vascular stiffening can alter the composition of arterial wall. During this process the low density Lipoprotein (LDL) can permeate into disrupted endothelium, where it can be oxidized. Oxidized LDL can attract leukocytes in the intima region that get scavenged by macrophages leading to formation of foam cells. During CAD there is change in structural protein known as elastin and α, β-integrins which are responsible for maintaining artery.[3,4,5,6]

Moreover, arterial stiffness is also caused by advanced glycation end products (AGEs), were it forms irreversible cross-links between long-lived proteins such as collagen. Elastin molecules are found to be susceptible to AGE cross-linking as it reduces the elastic matrix of the wall. AGE quenches nitric oxide and increases the generation of oxidant species such as peroxynitrite and may increase the Nf-kB inflammatory response, which affects the endothelial cell function.[4,7,8,9]

The hypothesis in this study is that ASA therapy might induce HDAC protein and by acetylating at multiple lysine sites it can induce elastin.

## MATERIALS AND METHODS

HL1 cardiomyocytes were incubated with either 50 μM and 0.25 mM ASA (in absolute alcohol) for 48 h in the same medium. Normal HL1 cells were treated with alcohol alone. At the ceassation of the treatment period, the medium was discarded and the cells were rinsed with PBS and harvested in Trizol® reagent (Invitrogen, Carlsbad, CA) for RNA isolation. ASA and all other chemicals were procured from Sigma-Aldrich Chemical Co. (St Louis, MO). HL1 cells were from ATCC, Manassas, VA.

## RESULTS AND DISCUSSION

Elastin is known to be a very essential protein that is responsible to maintain the property of the blood vessels, arteries. It is a structural matrix protein that is expressed by vascular smooth muscle cells in large vessels. Vascular stiffness may also be modulated by adhesion molecules.[2]

Here we assume that HDAC might deacetylate and activate elastin, that can prevent arterial stiffening and restore the property of artery. As elastin has multiple lysine (K) sites in its sequence HDAC might deacetylate it at its K site.

**The Sequence of Elastin [Homo Sapiens] protein is given as follows PDBID**

MAGLTAAAPRPGVLLLLLSILHPSRPGGVPGAIPGGVPGGVFYPGAGLGALGGGALG PGGKPLKPVPGGL

AGAGLGAGLGAFPAVTFPGALVPGGVADAAAAYKAAKAGAGLGGVPGVGGLGVS AGAVVPQPGAGVKPGK

VPGVGLPGVYPGGVLPGARFPGVGVLPGVPTGAGVKPKAPGVGGAFAGIPGVGPFG GPQPGVPLGYPIKA

PKLPGGYGLPYTTGKLPYGYGPGGVAGAAGKAGYPTGTGVGPQAAAAAAAKAAA KFGAGAAGVLPGVGGA

GVPGVPGAIPGIGGIAGVGTPAAAAAAAAAAKAAKYGAAAGLVPGGPGFGPGVVG VPGAGVPGVGVPGAG

IPVVPGAGIPGAAVPGVVSPEAAAKAAAKAAKYGARPGVGVGGIPTYGVGAGGFPG FGVGVGGIPGVAGV

PSVGGVPGVGGVPGVGISPEAQAAAAAKAAKYGVGTPAAAAAKAAAKAAQFGLVP GVGVAPGVGVAPGVG

VAPGVGLAPGVGVAPGVGVAPGVGVAPGIGPGGVAAAAKSAAKVAAKAQLRAAA GLGAGIPGLGVGVGVP

GLGVGAGVPGLGVGAGVPGFGAGADEGVRRSLSPELREGDPSSSQHLPSTPSSPRVP GALAAAKAAKYGA

AVPGVLGGLGALGGVGIPGGVVGAGPAAAAAAAKAAAKAAQFGLVGAAGLGGLG VGGLGVPGVGGLGGIP

PAAAAKAAKYGAAGLGGVLGGAGQFPLGGVAARPGFGLSPIFPGGACLGKACGRK RK

Instengan et.al (1999) reported that in SHR, alteration in elastins and integrins increases peripheral resistance and blood pressure which is also age dependent process.[10,12]

The findings suggests that elastin gene expression in HL1 cardiomyocytes is at its highest after aspirin drug treatment (4.13±0.06) at 50µm ASA, (3.03 ±0.003) at 0.25 mM ASA for 48 h compared to control counterpart. Reports also suggests that antihypertensive therapy can revert vascular growth. The drug irbesartan had a reducing effect on wall stiffness. They have

also revealed that increase in elastin protein can diminish vascular stiffness of spontaneous hypertensive rats (SHR).[11] Histone deacetylases [HDAC] are protein that deacetylates and activates various transcriptional proteins.[13] An increase in elastin protein might indicate an increase in HDAC protein.

Further, we deduce the Biomathematical Equation for Hemodynamic Pressure. The equation discusses that in both normal and artherosclerotic model the influence of inertial and viscous flow changes with arterial stiffening.

**According to Newton's Equation**

$\eta = (\bar{F}/A) / (\Delta V_y/\Delta Z)$ or                  But., $\bar{F} = M \times A$,   F net =Net Force,  M= Mass

A= Acceleration

$\eta = (\bar{F}/A) / (dV_y/dz)$

The blood flow is determined by layer's that arises and moves at different velocities, and fluid's viscosity arises from shear stress between the layer's that ultimately opposes any applied force.

**According to Reynolds Equation**

The force or flow of Blood:  Re= $\delta$ $\bar{v}$ r/$_\eta$     $\delta$ = Density, $_\eta$ = Viscosity, R=Radius of Artery,

V= $\bar{\text{A}}$verage Velocity of Blood

**Normal**

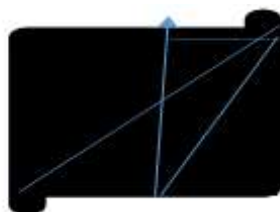If blood flow increases, than there is increase in inertial flow and viscous force is less.

**Artherosclerosis**

Blood flow decreases with a decrease in inertial flow and viscous force is more.

Shear stress increases between two layers is directly proportional (α) to velocity gradiant.

Thus, T= μ d́V/ d́Y            T= Turbulance,

Viscosity = $\mu / \S$

Blood flow = $I_f > V_f$,

Blood flow $\gg I_f < V_f$,

Blood flow $\alpha\ I_f \times 1/V_f$

Blood flow = $K.\ I_f \times 1/V_{f,\ therefore,}\ K = V_f / [Blood\ flow]\ [I_f]$

In Coronary Artery Diseases (CAD)

$(\vee)$Blood Flow $< (\vee)\ I_f < V_{f\ (\wedge)}$ and Turbulant Stress increases (more hemodynamics pressure overload)

$1/k = V_f / I_f \times$ Blood flow          $\{I_f = I_f\ (0min) - I_f\ (1min)\}$

Substituting Reynolds equation we get, $V_f$ = viscosity of Blood,

$$\S = Density$$

$$r = Radius\ of\ artery$$

$R = [I_f\ (0min) - I_{f\,(}1min)\ ]\ /\ V_f \quad (\S\ \overline{v}\ r/_\eta)$

$R = [I_f\ (0min) - I_{f\,(}1min)] / \dfrac{(\S\ v\ r\ (dVy/dz)}{F/A}$

If Turbulance = $\mu\ d'V/ d'y$

Viscosity = $\mu /\S$      but,    $\mu = \dfrac{d'y}{d'V \times \S}$

$\S\ \overline{v}\ r = (F/A) \div \S\ v\ r\ (d'Vy/ d'z)$

$1/\S\ v\ r = (A/F) \div \S\ v\ r\ (d'Vy/ d'z)$

than, T = $(A/F) \div \dfrac{d'y}{d'_{V\ x}\ \S}\ [\S\ \overline{v}\ r\ (d'Vy/ d'z)]$

$T = (A/F) \div \dfrac{d'y}{d'_{V\ x}\ \S}\ [\S\ \overline{v}\ r\ (\Delta Vy/ \Delta\ z)] \times \dfrac{I_f\ (0min) - I_f\ (1min)}{v_f}$

## CONCLUSION

The study illustrates that ASA theraupatics interventions can imcrease elastin gene expression which suggests that it may improve vascular stiffening and normalize hemodynamic pressure. Further the equations have shown that how hemodynamic pressure is dependent upon the inertial force, viscous force and turbulance of blood and that is dependent on radius of artery.

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