Original Research Article

A Comparative Study of Endothelial Dysfunction in Essential Hypertension

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Abstract

Endothelium plays a fundamental role in the cardiovascular system, forming an interface between blood and adjacent tissues by regulating the vascular tone through the synthesis of nitric oxide, prostaglandins and other relaxing factors. Endothelial dysfunction is characterized by vasoconstriction, cell proliferation and shifting toward a proinflammatory and prothrombic state. In hypertension endothelial dysfunction may be involved in the initiation and development of vascular inflammation, vascular remodeling, and atherosclerosis and is independently associated with increased cardiovascular risk. Different conditions such as impaired vascular shear stress, inflammation and oxidative stress, activation of the renin angiotensin system have been described as important pathophysiological mechanisms involved in the development of endothelial dysfunction. The release of extracellular vesicles by neighboring cells in the vascular wall has emerged as an important regulator of endothelial function and with potential antihypertensive properties and beneficial effects by counteracting the hypertension mediated organ damage. Furthermore, macrovesicles are emerging as an innovative therapeutic approach for vascular protection, allowing the delivery of bioactive molecules, such as miRNA and drugs interacting with the renin angiotensin system.

Key words

Endothelial dysfunction, Hypertension, FMD.

Introduction

The endothelium can greatly influence the vascular tone and structure. The main endothelium-derived factor is nitric oxide (NO), which is a potent vasodilator. The mechanism responsible for endothelial alteration in essential hypertensives is the activation of an alternative pathway involving cyclooxygenase, which reduces NO availability through production of oxidative stress. In the presence of impaired NO availability a hyperpolarizing factor seems to act as a compensatory pathway to sustain endothelium-dependent relaxation. This compensatory pathway can be further depressed by the simultaneous presence of essential hypertension causing endothelial dysfunction. In healthy conditions the vasoconstrictor effect of endothelin-1 is partially blunted by endothelial (ET) - receptor mediated NO production, Reduced NO availability can increase the biological activity of endothelin-1 as, in essential hypertensives, where this protective mechanism is lacking [1].

An important mechanism involves the perturbation of the homeostatic balance between NO and reactive oxygen species. Increased reactive oxygen species can inactivate NO and produce peroxynitrite [2].

A key determinant of endothelial biology is the cell redox state, and a key molecule that mediates endothelial function is NO. Evidence indicates that a homeostatic balance between NO and Reactive Oxygen Species (ROS), such as superoxide anion and hydrogen peroxide, regulates cell redox and is necessary for normal endothelial function. The impairment in the capacity of the vessel to dilate in the presence of endothelial dysfunction reflects the increased oxidative stress due to an enhanced catabolism of NO caused by increased generation of superoxide anion [2].

Endothelial cells can also induce relaxation by causing hyperpolarization [3]. The endothelium dependent relaxation cannot be abolished by NO synthase antagonists, thus ruling out NO as responsible for this activity [3]. In addition, endothelial cells can produce Endothelial Derived Contracting Factors (EDCFs), including prostanoids (thromboxane A and prostaglandin H), oxygen free radicals and endothelin-1 (ET-1), which counteract the relaxing activity of NO. In addition, oxygen free radicals can impair endothelial function by causing NO breakdown.

Endothelial function can be assessed by studies on vascular reactivity performed in different vasculature. The classical approach is to locally stimulate or inhibit endothelial cells by administration of specific agonists or antagonists, both pharmacological and mechanical and to simultaneously evaluate vascular changes using a variety of techniques. Impaired response to acetylcholine, methacholine, bradykinin and substance P has been documented in the forearm vasculature of essential hypertensive patients compared to normotensive controls [4].

Methods to assess endothelial dysfunction

In the 1990s, high-frequency ultrasonographic imaging of the brachial artery to assess endothelium-dependent flow-mediated vasodilation (FMD) was developed.

The capacity of blood vessels to respond to physical and chemical stimuli in the lumen confers the ability to self-regulate tone and to adjust blood flow and distribution in response to changes in the local environment. Many blood vessels respond to an increase in flow, or more precisely shear stress, by dilating. This phenomenon is designated FMD. The endothelial cell membrane contains specialized ion channels, such as calcium-activated potassium channels, that open in response to shear stress [5, 6, 7]. The effect of potassium channel opening is to hyperpolarize the endothelial cell, increasing the driving force for calcium entry (there are no voltage-gated calcium channels in endothelial cells). Calcium activates an enzyme, endothelial nitric oxide synthase (eNOS), and the subsequent

generation of NO appears to account for FMD [8, 9].

Aim and objectives

- To study endothelial dysfunction in patients with essential hypertension attending MRIMS
- To correlate with severity of endothelial dysfunction

Materials and methods

Study design: Prospective observational study
Study area: Department of General Medicine, MRIMS.
Study period: May 2023 to June 2024
Sample size: 30 cases

Inclusion criteria

- All patients with essential hypertension (after ruling out secondary causes)
- All patients of either sex
- Age >45 years and <55 years
- All patients who give informed consent

Controls

All normotensives between the age of 45 and 55

Exclusion criteria

All patients with following:

- Smokers
- Coronary artery disease
- Diabetes
- Chronic kidney failure
- Congestive heart failure
- Peripheral vascular disease
- Hypothyroidism
- Hyperthyroidism
- Hyperhomocystenemia
- Hypercholesterolemia
- Pheochromocytoma
- Hypercortisolism
- Acromegaly
- Conn's syndrome
- All patients who refused to give consent.

Methodology

The Institutional Ethics Committee approval was taken. An informed consent of the patient was taken. This was a prospective observational study. The study was undertaken in the Department of General Medicine, MRIMS.

A detailed history was taken from the patient. History included the patient's name, age, gender, occupation, and address, chief complaints with duration of the illness.A detailed physical examination of all systems was done. All routine investigations were done along with the Brachial Artery Doppler.

Brachial artery doppler study

Ultrasound systems are equipped with vascular software for two-dimensional (2D) imaging, color and spectral Doppler, an internal electrocardiogram (ECG) monitor and a high-frequency vascular transducer. Timing of each image frame with respect to the cardiac cycle is determined with simultaneous ECG recording on the ultrasound system video monitor.

Image acquisition

The subject was positioned supine with the arm in a comfortable position for imaging the brachial artery. The brachial artery was imaged above the antecubital fossa in the longitudinal plane (**Figure – 1, 2, 3**). A segment with clear anterior and posterior intimal interfaces between the lumen and vessel wall is selected for continuous 2D grayscale imaging. In addition to 2D grayscale imaging, both M mode and A mode (wall tracking) can be used to continuously measure the diameter [10, 11, 12] yet these techniques may be more subject to error owing to tracking drift. During image acquisition, anatomic landmarks such as veins and fascial planes are noted to help maintain the same image of the artery throughout the study.

Diagnostic criteria

The diagnosis of hypertension according to JNC 8 criteria:

Minimum three recordings by sphygmomanometer
Systolic - =/ >140
Diastolic- =/>90

Other investigations were done to rule out secondary causes of hypertension.

Figure - 1: Ultrasound image of the brachial artery (longitudinally) at 8× magnification, 11-MHz transducer frequency annotated for anatomic landmarks.

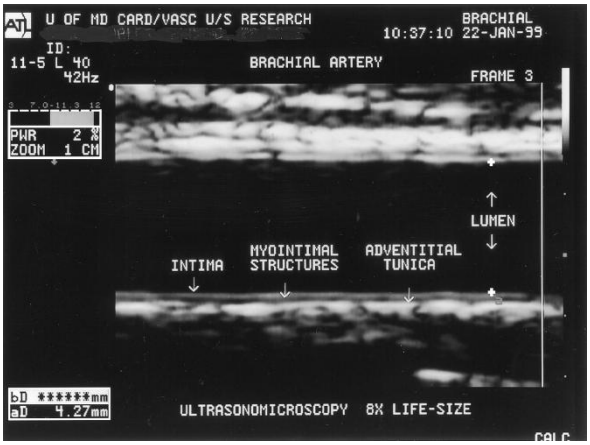
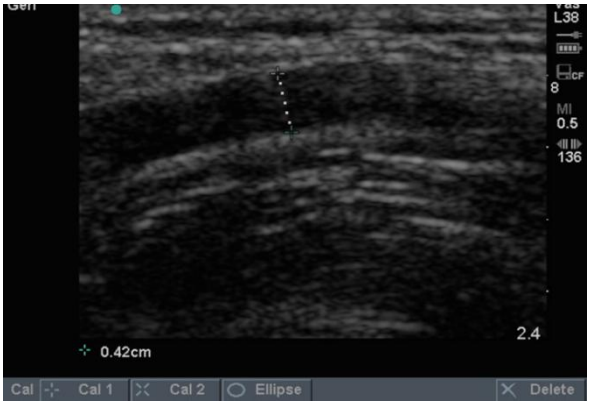


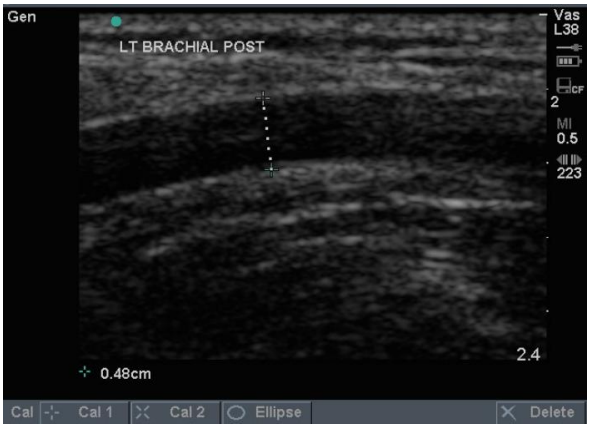
Figure – 2: Patient Mr. K. Pre Cuff Baseline Diameter of Brachial Artery.



Results and Discussion

Distribution of the study population based on Age was as per **Table – 1**. Distribution of the study population based gender as per **Table – 2**. Distribution of the study population based on Duration of Hypertension in years was as per **Table – 3**. Distribution of the study population based on FMD was as per **Table – 4**.

Figure – 3: Patient Mr. K. Post Cuff Brachial Artery Diameter.



Among the 30 patients studied, the age group varied from 46 - 55 yeas. 17 patients (56.6%) in the age group 46-50 years and 13 patients (43.4%) are in the age group 51-55 years. The mean age of cases was slightly higher (51.20 ± 4.63 years) compared to controls (49.86 ± 4.42 years), but this difference was not statistically significant (p=0.63). The balanced age distribution in this study ensures that age-related biases are minimized, allowing for a clearer assessment of other factors influencing endothelial function.

Gender distribution in the study population was equal, with both cases and controls comprising 53.3% males and 46.7% females. This parity is essential as it allows for a comprehensive analysis of endothelial dysfunction across genders. The current study's gender-balanced population ensures that the influence of gender on endothelial dysfunction can be accurately assessed, avoiding potential gender-specific biases.

The study revealed that a majority of the cases (60%) had hypertension for 5 years or less, while 40% had it for 6 years or more. This distribution highlights the chronic nature of hypertension in the study population and its potential impact on endothelial function.

Panda, et al. [13] (2020) emphasized that prolonged hypertension exacerbates oxidative stress and reduces nitric oxide availability,

further impairing endothelial function. The mean duration of hypertension in this study was 5.06 ± 1.95 years, indicating that a significant portion of the study population is experiencing early to mid-stage hypertension, which is crucial for understanding the progression of endothelial dysfunction and tailoring early intervention strategies.

Table - 1: Distribution of the study population based on Age.

	Cases		**Control**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
46 – 50	8	53.3%	9	60%	17	56.6%
51 – 55	7	46.7%	6	40%	13	43.4%
Total	15	100%	15	100%	30	100%
Mean Age	51.20 ± 4.63		49.86 ± 4.42		50.53 ± 4.56	

Table - 2: Distribution of the study population based gender.

	Cases		**Control**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
Male	8	53.3%	8	53.3%	16	53.3%
Female	7	46.7%	7	46.7%	14	46.7%
Total	15	100%	15	100%	30	100%

Table - 3: Distribution of the study population based on Duration of Hypertension in years.

	Frequency	**Percentage**
≤5	9	60%
≥6	6	40%
Total	15	100%
Mean duration	5.06 ± 1.95	

Table - 4: Distribution of the study population based on FMD.

	Cases	**Control**	**P value**
Mean FMD	10.32 ± 9.97	17.38 ± 9.91	0.0001*

Conclusion

Monitoring endothelial function through measures like FMD, alongside traditional risk factors, can provide valuable insights for early detection and management of cardiovascular risk. Future research should explore interventions targeting endothelial health, such as lifestyle modifications and pharmacological treatments, to prevent and mitigate cardiovascular diseases in hypertensive populations. By focusing on endothelial function, healthcare providers can better understand and address the multifaceted nature of cardiovascular risk, ultimately improving patient outcomes and reducing the burden of cardiovascular diseases.

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