Original Research Article

ASSESSING ENDOTHELIAL DYSFUNCTION THROUGH SHEAR STRESS: IMPLICATIONS FOR CARDIOVASCULAR HEALTH

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ABSTRACT

Background: Atherosclerosis, the precursor to many CVD forms, underscores the pivotal role of the vascular endothelium. Endothelial dysfunction, closely tied to conditions like coronary artery disease (CAD), hypertension, and diabetes mellitus, emerges as a critical clinical concern preceding histological signs of atherosclerosis. Within the vascular system, the equilibrium of vasodilatory and vasoconstrictor substances is paramount for vascular tone regulation, with nitric oxide (NO) showcasing significant vasodilatory effects. The endothelial response to increased shear stress results in an active release of vasoactive substances, crucial for vascular homeostasis. In cases of endothelial dysfunction, this delicate balance is disturbed, potentially leading to various vascular pathologies.

Materials and Methods: The study's investigational focus revolves around the potential of shear stress assessment in the brachial artery as a surrogate marker for cardiovascular risk. By evaluating shear stress through non-invasive means, the study aims to ascertain its feasibility as a cost-effective screening test for identifying cardiovascular disease risk.

Results: The data indicates that the shear stress values at both baseline and during hyperemia phases do not significantly differ between the Control and Case groups. This lack of statistical significance suggests that shear stress may not be a differentiating factor related to endothelial function or vascular health in this study. Other variables or factors may be more influential in distinguishing between the two groups regarding cardiovascular health and endothelial function.

Conclusion: The data indicates that the shear stress values at both baseline and during hyperemia phases do not significantly differ between the Control and Case groups. This lack of statistical significance suggests that shear stress may not be a differentiating factor related to endothelial function or vascular health in this study. Other variables or factors may be more influential in distinguishing between the two groups regarding cardiovascular health and endothelial function.

Keywords: Brachial Artery, Endothelial Dysfunction, Flow Mediated Dilation, Shear Stress, Hemodynamics.

INTRODUCTION

Cardiovascular disease (CVD) stands as the foremost cause of morbidity and mortality globally (World Health Organization, 2017).[1] Atherosclerosis, often the initial stage of various forms of CVD, underscores the critical role of the vascular endothelium. Endothelial dysfunction, linked to conditions like coronary artery disease (CAD), hypertension, and diabetes mellitus, represents a pivotal clinical concern prior to histological evidence of atherosclerosis.[2]

Under normal physiological conditions, a balance exists between vasodilatory (e.g., nitric oxide, prostacyclin, adenosine, and hydrogen peroxide) and vasoconstrictor substances (e.g., endothelin-1, angiotensin II, and thromboxane A2). Nitric oxide (NO), a potent vasodilator, plays a significant role in arterial tone regulation by activating cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells. The NO-cGMP pathway is activated when the healthy endothelium is stimulated by vasoactive substances or increased shear stress.[3]

The release of paracrine hormones is primarily stimulated by the frictional force of flowing blood, known as shear stress, along the endothelium. Any imbalance or impairment in these mediators can lead to endothelial dysfunction, disrupting the delicate regulation of vascular tone and contributing to various vascular pathologies.

Shear stress in an artery refers to the force exerted by the flowing blood perpendicular to the arterial wall.[2] It is the frictional force generated as blood moves through the blood vessels, causing a drag on the endothelial cells that line the artery. This shear stress is essential for endothelial function as it activates various mechanisms in the endothelial cells, including the release of vasoactive substances like nitric oxide (NO) and prostacyclin, which help regulate vascular tone and maintain vascular health. Proper shear stress is crucial for the normal functioning of the endothelium and plays a significant role in cardiovascular health.[4,5]

This study seeks to provide evidence on whether assessing shear stress in the brachial artery holds potential as a surrogate marker for cardiovascular disease risk. Additionally, the feasibility of using this method as a cost-effective, non-invasive screening test to identify cardiovascular disease risk will be evaluated, considering that invasive approaches like angiography and computed tomographic angiography (CTA) are associated with high costs and potential health risks.[6,7] This exploratory study will involve a large sample size within a planned setup to shed light on the future prospects of this investigative method.

MATERIAL AND METHODS

The data collection procedure for ultrasonographic scanning of the brachial artery followed a systematic approach to ensure accurate and comprehensive data acquisition. This involved obtaining informed consent and noting details such as age, sex, cardiovascular history, medication use, and the presence of risk factors. The procedure occurred in a quiet, temperature-controlled environment ranging from 22-26 °C.[2]

Initially baseline measurements were taken. The subject laid supine on an exam table with a 3-lead EKG attached, and blood pressure was measured after a 5-minute rest period. A tourniquet cuff was applied in a proximal position on the upper arm for cross-sectional scanning of the brachial artery using colour flow imaging. Various adjustments were made to optimize visualization and accurately record the baseline velocity using 2D Doppler mode.

The cuff was inflated above systolic blood pressure, and meticulous monitoring was conducted using 2D-Doppler imaging to capture the time of cuff release, which is crucial for measuring time to peak diameter during data analysis.

Then the cuff was released and the measurements in the stage of hyperaemia were taken.

Careful adjustments were made for arterial shifts while monitoring the artery using B-Mode ultrasonography. The probe position and angle were modified to optimize intima-media thickness visualization (double lines of pignoli), and diameter measurements were meticulously recorded for the specified duration. [Figure 1]

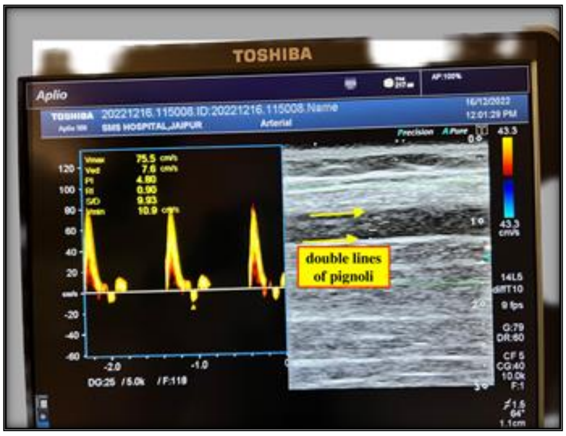

Figure 1: Measurments in Doppler Scan (double lines of pignoli)

The precise and detailed approach ensures the collection of following valuable data in both baseline and hyperaemic stages for analysing parameters-

1. Mean Velocity (cm/sec): The average arterial velocity of blood in the middle 50% of the lumen during one cardiac cycle, estimated from Doppler spectral waveforms. It is proportional to blood flow and inversely proportional to cross-sectional area.
2. Diameter (mm): The intima-intima distance measured from a longitudinal view along the vessel axis. This measurement is taken at both Baseline and during reactive hyperaemia.

3. Flow (ml/min): The bulk flow of fluid in the circulation, calculated from mean velocity and diameter using the equation:
Mean Flow (ml/min) = mean velocity × π × (diameter/2)^2
4. % FMD: The percentage change in arterial diameter after occlusion in response to hyperaemia, relative to the baseline diameter.
5. Shear Stress (dynes/cm2): The frictional force exerted by circulating blood on the intima surface, determined by velocity and inversely proportional to diameter, calculated by the formula:
Shear Stress (dynes/cm2) = 8 × μ × mean velocity / diameter
μ = 0.035 poise (blood viscosity)

These parameters provide valuable insights into the hemodynamic characteristics of the brachial artery and can help in assessing endothelial function and cardiovascular health. The utilization of a Microsoft Excel 2010 worksheet facilitated the comprehensive compilation of data to intelligently present quantitative figures such as mean and standard deviation. The qualitative data portrayal in percentage added depth to the insights drawn. Through unpaired 't' tests and chi-square tests, the significance of differences in mean values and proportions was rigorously assessed, with a significance level of $p < 0.05$ underscored as the threshold for statistical significance.

Table 1: Mean Shear stress at wall (dynes/cm2) ± Sd of Control and Case group subjects

Parameters	Group		P-value	Significance
	Control (n=70)	Case (n=70)		
Shear stress at wall (dynes/cm2) Baseline	38.11 ± 10.20	43.14 ± 20.40	> .05	NS
Shear stress at wall (dynes/cm2) Hyperemia	38.69 ± 10.60	40.34 ± 17.98	> .05	NS

Table 2: Comparison of Study Data

Characteristics	Alley H et al. (2014)[2]	Bellien et al. (2010)[3]	Verma I et al. (2017)[9]	Tatsua Maruhashi et al. (2020)[8]	Result Present Study (2024)
Subjects (cases)	25 (PAD)	24 (diabetic)	35 (RA)	5735 (risk cases for CVD)	70 (CVD)
Subjects (control)	25	24	25	1542	70
Age (case)	68 ± 6	34±3	46.0 ± 9.1	53.3± 10.3	57.83 ± 6.95
Age (control)	68 ± 11	37±3	42.8 ± 7.6	44.5± 9.8	39.00 ± 12.28
BMI (case)	29 ± 7	24.5±0.8	24.1 ± 3.9	24.0 3.3	23.69 + 2.45
BMI (control)	30 ± 4	23.7±0.8	23.2 ± 2.6	21.8 2.8	24.36 ± 2.40
Sys BP (case)	139	118	125	130	130
Sys BP (control)	134	118	118.8	117.1	114.2

Table 3: Comparison of haemodynamic data

Parameter	Alley H et al. (2014)		Present study	
	Case Group (Mean±SD) n=25	Control Group (Mean±SD) n=25	Case Group (Mean±SD) n=70	Control Group (Mean±SD) n=70
Baseline Artery Diameter (mm)	4.11 ± 0.60	4.29 ± 0.53	3.44+0.67	3.27+ 0.54
Baseline Velocity (cm/sec)	18 ± 6	16 ± 5	49.46 ± 16.10	49.68 ± 9.94
Baseline Flow (ml/min)	2.52 ± 1.4	2.3 ± 0.78	4.45 ± 1.55	5.45 ± 1.46
Baseline Shear Stress (dynes/cm2)	13 ± 5	11 ± 3	43.14 ± 20.40	38.11 ± 10.20
Reactive Hyperaemia Diameter (mm)	4.38 ± 0.60	4.68 ± 0.55	3.59+0.69	3.42+ 0.71
Reactive Hyperaemia Velocity (cm/sec)	70 ± 25	78 ± 27	48.94 ± 14.78	56.88 ± 12.46
Reactive Hyperaemia Flow (ml/min)	10.97+ 5.45	13.53 ± 5.7	4.88 ± 1.53	7.89 ± 2.13
Reactive Hyperaemia Shear Stress (dynes/cm2)	46 ± 19	47 ± 18	40.34 ± 17.98	38.69 ± 10.60
Brachial FMD (%)	6.8 ± 3.5	9.1 ± 3.6	5.50 ± 2.30	12.3 ± 1.69

RESULTS

Shear stress in an artery refers to the force exerted by the flowing blood perpendicular to the arterial wall. It is the frictional force generated as blood moves through the blood vessels, causing a drag on the endothelial cells that line the artery. This shear stress is essential for endothelial function as it activates various mechanisms in the endothelial cells, including the release of vasoactive substances like nitric oxide (NO) and prostacyclin, which help regulate vascular tone and maintain vascular health. Proper shear stress is crucial for the normal functioning of the endothelium and plays a significant role in cardiovascular health.

The study results revealed significant findings in various parameters between the Control and Case groups. Significant differences were observed in the Blood Sugar Levels, with the Case group exhibiting substantially higher mean levels compared to the

Control group, as indicated by a p-value of less than .001. In contrast, the Baseline Artery Diameter did not exhibit a significant difference between the groups, with a p-value greater than 0.05. Similarly, the Mean Velocity showed no statistically significant variation between the Control and Case groups, with a p-value exceeding 0.05. Conversely, a significant difference was noted in the % FMD values, with the Case group displaying significantly lower % FMD compared to the Control group, denoted by a p-value of less than .001.

The shear stress at the wall during the hyperaemia phase did not exhibit a statistically significant difference between the Control and Case groups, with a p-value exceeding 0.05. Overall, these results highlight variations in Blood Sugar levels and % FMD between the groups, suggesting potential differences in endothelial function and vascular health, while parameters like Artery Diameter and Velocity did not show significant disparities.

DISCUSSION

Celermajer DS5 first devised a non-invasive method for testing endothelial function to identify abnormalities in symptom-free young individuals at high risk of atherosclerosis. This technique involves using high-resolution ultrasonography to measure conduit artery diameter, typically the brachial artery, in response to elevated blood flow and shear stress following limb ischemia. Flow-mediated dilation (FMD) represents the relative change in artery diameter from the baseline.

The investigation into endothelial function and its association with cardiovascular disease risk presents compelling insights drawn from a comparative analysis of multiple studies.[10,11] Notably, the study delves into the impact of shear stress on endothelial homeostasis and the subsequent implications for cardiovascular health. The meticulous assessment of endothelial function using Shear Stress has unraveled significant disparities in vascular function between distinct patient cohorts, shedding light on crucial cardiovascular risk factors as said in study of Atkinsons et al in 2015.[12] In present study, the shear stress at the wall during the hyperaemia phase did not exhibit a statistically significant difference between the Control and Case groups.

Tatsua Maruhashi et al. and Alley H et al. exhibited varying gender insights, emphasizing optimal FMD cutoff values differently for both genders. Verma S et al. and Tatsua Maruhashi et al,[8] provided valuable analyses on optimal FMD cutoff values across different age brackets and age decades. The distribution of subjects, especially the predominance of over-50-year-olds, showcases demographic nuances influencing cardiovascular health. Many studies have been conducted taking groups of various age and conditions. Similarly, Lars Lind conducted a cohort study in 2014 on flow-mediated vasodilation over five years in the general elderly population and its relation to cardiovascular risk factors.[13] Birk, G. et al evaluate role of shear stress by finding brachial artery adaptation in lower limb exercise training in 2012.[14] Casey et al in 2012 found contribution of alpha-adrenergic vasoconstriction towards age-related increase in conduit artery retrograde and oscillatory shear.[15] Cecchi E. et al in 2011, evaluate the role of hemodynamic shear stress in cardiovascular disease.[16]

Doshi SN, et al. assessed flow-mediated dilatation following wrist and upper arm occlusion in humans They wanted to assess the contribution of nitric oxide.[17] In present study non-invasive flow mediated dilatation was assessed on brachial artery doppler imaging using ultrasonography (B mode).

The observed significant differences in Blood Sugar Levels and % FMD values between the study groups emphasize key variations in endothelial functionality and cardiovascular health profiles. The non-significant variances in Artery Diameter and Velocity provide additional context to the complex interplay of factors impacting vascular health in distinct patient cohorts. These discrepancies underscore the need for tailored interventions and further explorations in endothelial function assessment.

CONCLUSION

In summary, while shear stress is a fundamental parameter in endothelial function evaluation18,19, its lack of significant differences in this study necessitates a more nuanced and multi-dimensional approach to effectively capture the complexities of cardiovascular health and vascular dynamics. Further research integration and exploration of complementary markers alongside shear stress could lead to a more robust and detailed understanding of endothelial function and cardiovascular risk assessment.

Recommendations

Further investigation into shear stress at the wall in response to different cardiovascular stimuli could enhance understanding of its role in endothelial function. This could involve studies focusing on the impact of exercise, dietary changes, or pharmacological interventions on shear stress and its relation to cardiovascular health.

REFERENCES

1. World Health Organization. (n.d.). Cardiovascular diseases (CVDs). Retrieved from WHO Fact Cardiovascular Diseases.
2. Alley H et al. Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery in Clinical Research. J. Vis. Exp. 2014; (92), e52070. doi:10.3791/52070.
3. Bellien et al. Early stage detection of conduit artery endothelial dysfunction in patients with type 1 diabetes. Diabetes & Vascular Disease Research. 2010; 7(2) 158–166.
4. Celermajer DS, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. The Lancet. 1992; 340:1111–1115.

5. Holder, S.M., Dawson, E.A., Brislane, Á., Hisdal, J., Green, D.J., & Thijssen, D.H.J. Fluctuation in shear rate, with unaltered mean shear rate, improves brachial artery flow-mediated dilation in healthy, young men. Journal of Applied Physiology 2019; 126(6): 1687-1693. doi: 10.1152/japplphysiol.00009.2019.
6. Verma S, Wang CH, Lonn E, Charbonneau F, Buithieu J, Title LM, Fung M, Edworthy S, Robertson AC, Anderson TJ; FATE Investigators. Cross-sectional evaluation of brachial artery flow-mediated vasodilation and C-reactive protein in healthy individuals. Eur Heart J. 2004 Oct;25(19):1754-60. doi: 10.1016/j.ehj.2004.06.039. PMID: 15451155.
7. Priyanka Katara et al. Assessing Endothelial Function: Flow-Mediated Dilation as a Surrogate Marker for Cardiovascular Disease Risk. Journal of Cardiovascular Disease Research. 2024; 15(05):121-7. https://jcdronline.org/paper.php?slug=assessing-endothelial-function-flow-mediated-dilation-as-a-surrogate-marker-for-cardiovascular-disease-risk
8. Maruhashi, Tatsuya et al. Diagnostic Criteria of Flow-Mediated Vasodilation for Normal Endothelial Function and Nitroglycerin-Induced Vasodilation for Normal Vascular Smooth Muscle Function of the Brachial Artery. Journal of the American Heart Association 2020; 9(2): e013915. doi:10.1161/JAHA.119.013915
9. Verma I et al. Predictors of endothelial dysfunction and atherosclerosis in rheumatoid arthritis in Indian population. Indian Heart Journal 2017; 69(2): 200-06. https://doi.org/10.1016/j.ihj.2016.10.013.
10. Neunteufl T, et al, Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. Atherosclerosis. 1997 Feb 28;129(1):111-8.
11. Thijssen, D.H.J., Bruno, R.M., Van Mil, A., Holder, S.M., Faita, F., Greyling, A. et al. Expert consensus and evidence-based guidelines for the assessment of flow-mediated dilation (FMD) in humans. European Heart Journal 2019; 40(30): 2534-2547. doi: 10.1093/eurheartj/ehz350.
12. Atkinson, C. L., Carter, H. H., Naylor, L. H., Dawson, E. A., Marusic, P., Hering, D., Schlaich, M. P, Thijssen, D. H. & Green, D. J. Opposing effects of shear-mediated dilation and myogenic constriction on artery diameter in response to handgrip exercise in humans. Journal of Applied Physiology 2015; 119: 858-64.
13. Lars Lind. Flow-mediated vasodilation over five years in the general elderly population and its relation to cardiovascular risk factors. Atherosclerosis. 2014 December; 237(2): 666-670.
14. Birk, G. K., Dawson, E. A., Atkinson, C., Haynes, A., Cable, N. T., Thijssen, D. H. & Green, D. J. Brachial artery adaptation to lower limb exercise training: role of shear stress. Journal of Applied Physiology 2012; 112: 1653-8.
15. Casey, D. P., Padilla, J. & Joyner, M. J. alpha-adrenergic vasoconstriction contributes to the age-related increase in conduit artery retrograde and oscillatory shear. Hypertension 2012; 60: 1016-22.
16. Cecchi, E., Giglioli, C., Valente, S., Lazzeri, C., Gensini, G. F., Abbate, R. & Mannini, L. Role of hemodynamic shear stress in cardiovascular disease. Atherosclerosis 2011;214: 249-56.
17. Doshi SN, et al. Clinical science. Vol. 101. London, England: 2001. Flow-mediated dilatation following wrist and upper arm occlusion in humans: the contribution of nitric oxide; pp. 629–35.
18. Cheng, J. L., Au, J. S. & Macdonald, M. J. Peripheral artery endothelial function responses to altered shear stress patterns in humans. Exp Physiol 2019; 104: 1126-35.
19. Chiu, J. J., Usami, S. & Chien, S. Vascular endothelial responses to altered shear stress: pathologic implications for atherosclerosis. Annals of Medicine 2009; 41: 19-28.