A Mechanical for Growth of Atherosclerotic Plaque

[1]SSSR Sarathbabu Duvvuri
[1]Professor
Department of Electrical & Electronics Engineering
Shri Vishnu Engineering College for Women Bhimavaram
Bhimavaram, Andhra Pradesh, India - 534202
Email: sarath.duvvuri@svecw.edu.in
ORCID ID:- https://orcid.org/0000-0001-9653-2519

[2]Nookala Nanda Kumar
[2]Senior Associate
Cognizant Technology Solutions
Hyderabad, Telangana, India
Email: nanda.819@gmail.com

[3]Mohan Anand
[3]Associate Professor
Department of Chemical Engineering
Indian Institute of Technology Hyderabad
Hyderabad, Telangana, India

***Abstract*—Atherosclerotic plaque growth is known to be positively correlated with low oscillatory wall shear stress. We identified several articles containing data for intimal thickening in atherosclerotic arteries, and compiled them in a consistent manner to relate (non-dimensional) thickness and mean wall shear stress. An improved exponential equation with better R square value than previous equations is formulated to correlate the compiled data. Parameters such as age and kinetics of smooth muscle cell growth are excluded from the model. The proposed mathematical model can be implemented in computational aid dynamics studies that aim to estimate thickening of artery wall based on mechanical variables alone**.

Keywords: Atherosclerotic; Arteries; Low-Density Lipids (LDL); Non-axial Flow.

I. INTRODUCTION

Atherosclerosis occurs due to deposition of excess low-density lipids (LDL) beneath the endothelial layer of the artery. Thus, the blood vessel walls become thicker and stiffer, narrowing the artery lumen and obstructing the flow, which changes the dynamics of flow within the artery. Many angiographic techniques show evidence for atherosclerosis progression in arteries [11]. The aorta and the coronary arteries are most often affected. Hemodynamic factors regulate atherogensis and influence both the growth of plaque and the final cross-sectional shape of the artery lumen. It is proved that mechanical variables, namely non-axial flow and pulsatile wall shear stress, which manifest as changes in mechanical force on the endothelial cells are the primary contributors to atherosclerosis progression [15], [12], [8]. The currently accepted hypothesis is summarized in [12] who state that atherosclerotic plaque growth and endothelial cell damage are a function of shear stress on the wall of arteries: shear

stress > 1.5 P_a in arteries deactivates endothelial damage and diminishes plaque growth, whereas shear stress < 0.4 P_a stimulates the growth of Plaque by inducing an atherogenic phenotype.

It is necessary to develop a correlation between wall thickening and wall shear stress to predict the blockage due to plaque growth in flow simulations. However, wall shear stress varies with Reynolds number, Womersley number, and size (percentage) of stenosis (see [10] & [13]) as also stenosis length (see [14]) in simulations of blood flow. Hence, a good correlation for plaque growth should compile data separately from each arterial location and non-dimensionlize them consistently. Here we briefly review the literature of such correlations/models for each location before proceeding to develop a new correlation using an expanded data set at the abdominal aortic bifurcation and coronary artery.

II. REVIEW OF LITERATURE

Friedman et al [4] were the first to propose a purely mechanical model to estimate intimal thickening in human aorta. In physiologically realistic pulsatile flow conditions, they used a Laser Doppler Anemometer to measure velocity of blood flow through a cast of abdominal aortic bifurcation (abdominal aorta branching into two iliac arteries). They then plotted the data for wall thickness versus pulse shear rate (defined as the difference between maximum and minimum shear rate in a cycle) and pulse shear stress (for in-vivo blood viscosity), and suggested a linear model to fit the data. They further refined the model in [5] where intimal thickness varies exponentially (not linearly) with maximum shear rate: age is also included as factor in the model. The data suggest that at early stages the intimal thickness is higher at sites exposed to high shear stresses. However, ultimately the increase in intimal thickness is highest at sites exposed to low shear stress. [1] used laser photo chromic dye tracer technique in an in-vitro model based on CT scans of diseased abdominal aorta, and developed a linear correlation (R2 = 0.309) between normalized intimal thickness and mean wall shear stress at normal (resting) flow condition. [9] correlated data for plaque growth in abdominal aortic bifurcation with wall shear stress measured during flow of Newtonian and Non-Newtonian (power law) blood analogs in an identical cast of the bifurcation. A linear model is proposed but the data for plaque growth is inconsistent with the currently accepted hypothesis of increased thickness for lower wall shear stress. A negative correlation between intimal thickening and wall shear stress for minimally diseased artery was develop by [6] for plaque in the coronary artery. They collected data using Laser Doppler Anemometer and suggested both linear as well as exponential models to fit the data. Friedman et al [3] used data from coronary arteries to improve his previous baseline model in6 [4], and included the kinetics of smooth muscle cell migration, proliferation, metabolism, expression of extracellular matrix, lipoprotein kinetics and binding etc, and developed a model for variation of intimal thickening with shear rate. Experimental data was obtained for plaque progression in coronary artery by [7] which showed a correlation between vessel wall shear stress and atherosclerosis progression. They concluded that low shear stress significantly increases the rate of atherosclerosis progression in coronary artery. Many of the above works suggested that linear regression model is the best fit for intimal thickening due to the extensive scatter in the data. While Friedman and co-workers got good data for intimal thickening, they correlated it with wall shear rate (possibly in line with the hypothesis at that time) instead of wall shear stress. Recent data of [1] correlated thickening with wall shear stress but there is extensive scatter, and only linear model was proposed. We therefore decided to combine data from above sources from both the abdominal aortic bifurcation and the coronary artery to see if a better correlation could be developed which reflects our current understanding of atherosclerosis i.e. that intimal thickening is related to wall shear stress & its oscillatory nature. We tried different regression models available in MATLAB R2023a curve fitting tool to determining the best fit.

III. MODEL FOR PLAQUE GROWTH VERSUS WALL SHEAR STRESS

We first compiled a set of data points relating intimal thickening in the abdominal aorta wall with wall shear stress measurements; we also compiled the data for coronary arteries. The compiled data points are shown in Figure 1, and we wanted to use these to obtain a purely mechanical model for plaque growth. The extensive scatter and clearly different spread of the two data sets suggest that it is not possible to get a model correlating all the data. The compiled data is therefore split into two separate categories one for abdominal aortic bifurcation and-another for coronary arteries, and separate correlations are reported for each.

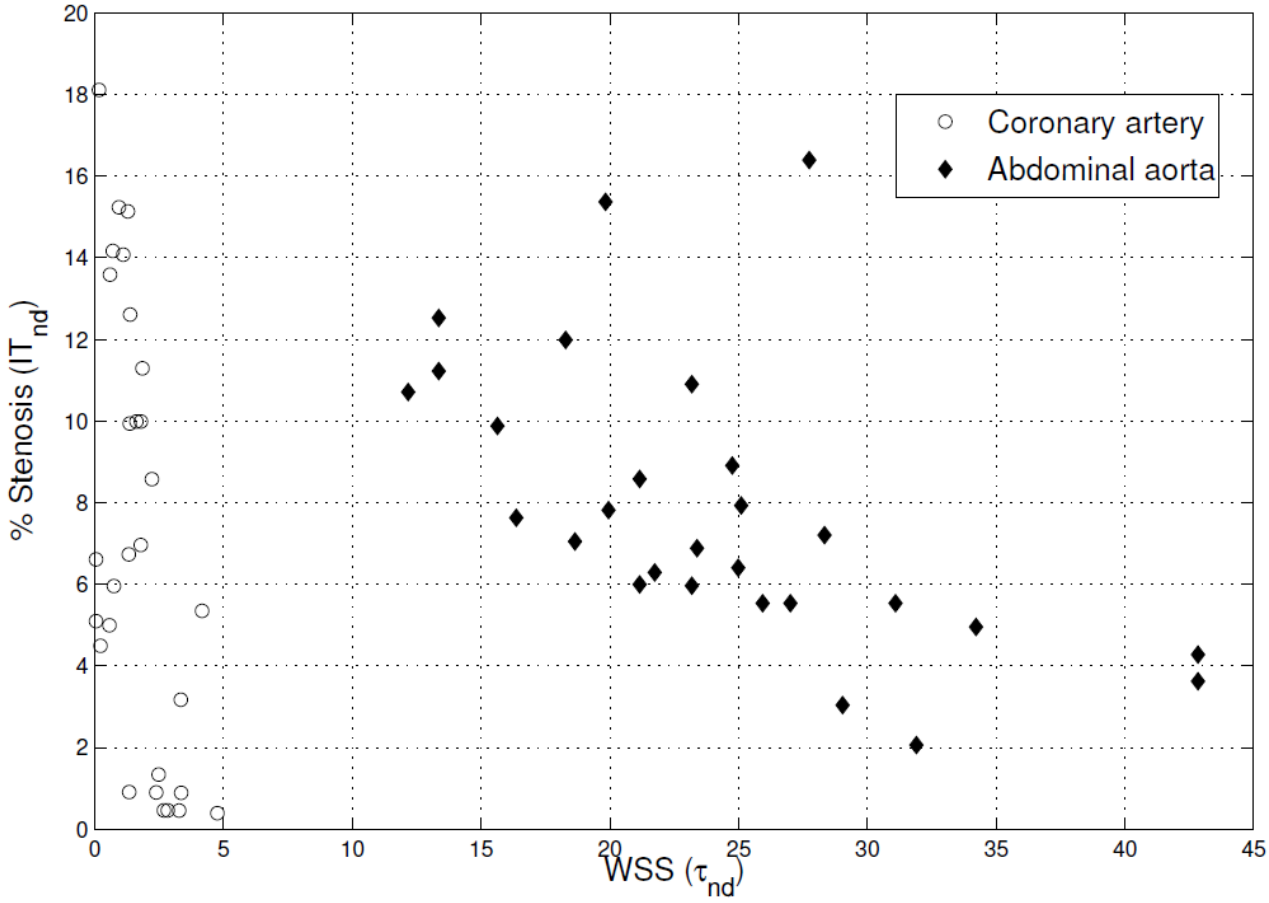

Figure 1: Experimental data for non-dimensional intimal thickness versus (non-dimensional) wall shear stress.

We were unable to obtain the wall shear stress data in [5] since the mean shear rate is not reported in those experiments. The data in [9] runs counter to the currently held hypothesis and was excluded. We compiled the data only from [1] and [4] for the purpose of correlation of plaque growth in the abdominal aortic bifurcation. We extracted intimal thickness data in [4] and non-dimensionalized it, using the (hydraulic) radius (R) of 9.35mm for abdominal aorta in [1]; the corresponding mean wall shear stress was calculated to be 14% of pulse shear rate reported for Newtonian blood analog of 4.2 centipoise viscosity. The data relating normalized intimal thickness and mean wall shear stress obtained in [1]: the same aorta radius of 9.35mm was used to non-dimensionalized intimal thickness data. The dimensional mean wall shear stress data were converted non-dimensionalized using the following

equation: $\tau_{nd} = \frac{\tau_d}{\mu U / R}$ (Here U is obtained from Reynolds Number reported, and viscosity (μ) is 4.2 centipoise as before.

The curve fitting tool box in MATLAB R2023a is used for finding a better equation than a linear curve fit for the data. An exponential equation is determined and is given by:

$$IT_{nd} = 18.21e^{(-0.03613\,\tau_{nd})} \quad (1)$$

Where $IT_{nd} = \%$ stenosis $\left(\frac{IT}{R}100\right)$, and τ_{nd} is the non-dimensional mean wall shear stress. The R^2 value of 0.345 obtained for the linear equation in [1] and this is seen in Figure 2.

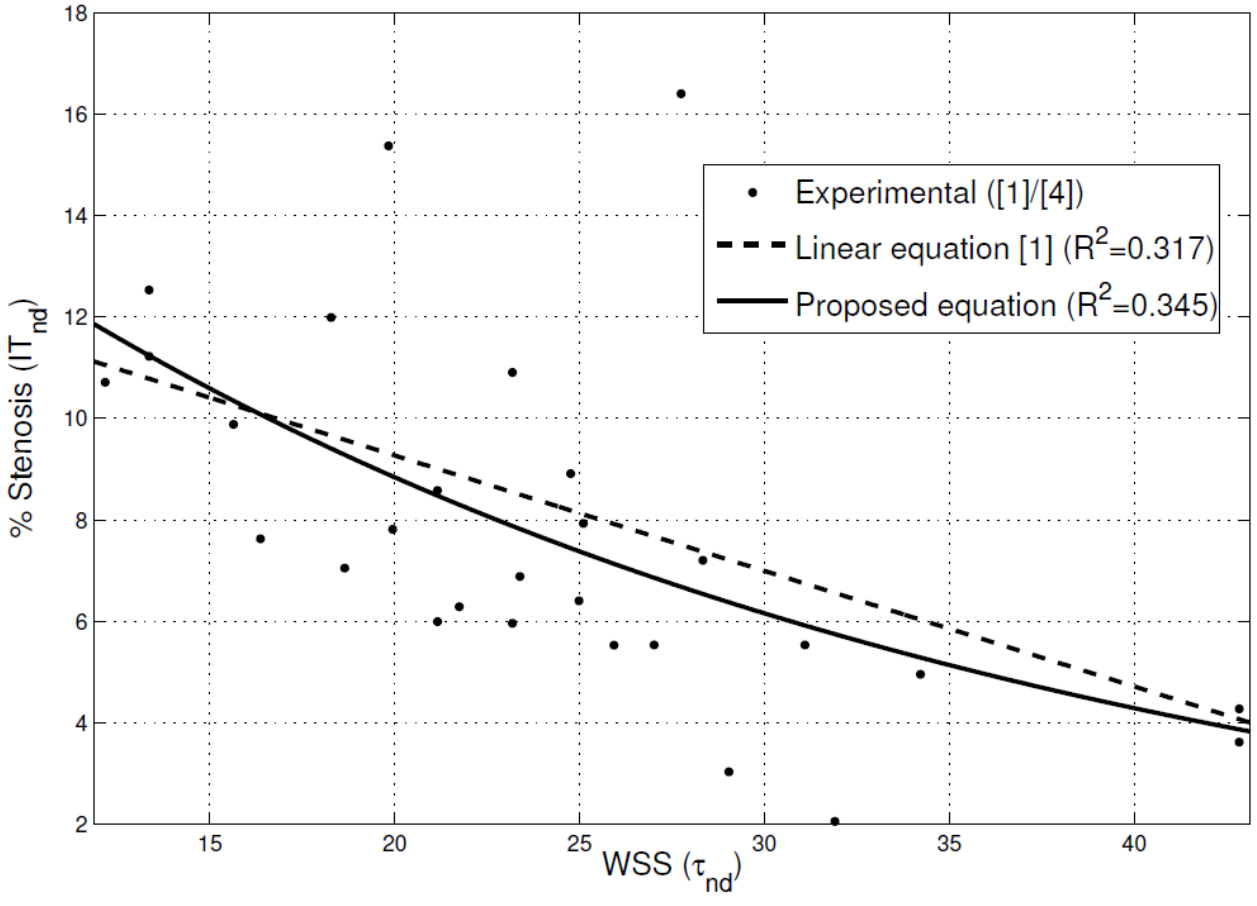

Figure 2: Variation of intimal thickening with mean wall shear stress for abdominal aorta.

Similarly for the case of coronary artery, we compiled the data from [7] and [6] for developing a correlation. The non-dimensionalized data of % stenosis and mean wall shear stress is obtained based on hydraulic radius of coronary artery (2 mm) and mean flow rate of (3.9 ml/s) blood having 4.2 centipoise viscosity. The compiled data are shown in Figure 3 and the proposed exponential fit is:

$$IT_{nd} = 11.86e^{(-0.3202\,\tau_{nd})} \quad (2)$$

Where $IT_{nd} = \%$ stenosis and τ_{nd} is the non-dimensional mean wall shear stress. The R^2 value of

0.281.

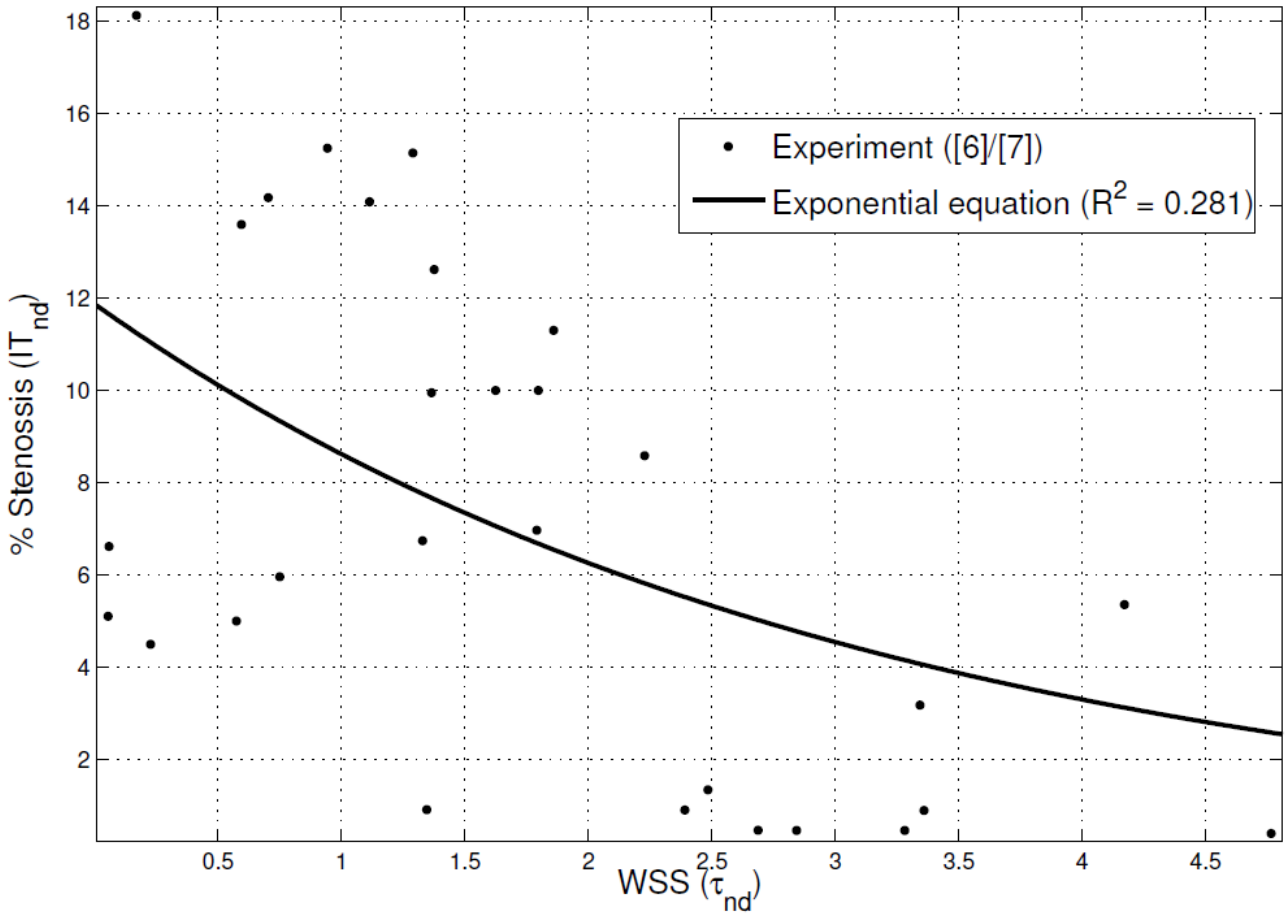

Figure 3: Variation of intimal thickening with mean wall shear stress for coronary artery.

IV. CONCLUSION & FUTURE DIRECTION

Data for intimal thickening reported at the abdominal aortic bifurcation and coronary artery are collected from various sources, and plotted versus with data for mean wall shear stress at those sites in order to develop a purely mechanical model for intimal thickening. Earlier work correlated thickening with shear rate or stopped with a linear correlation due to extensive data scatter. By compiling data from several sources in a consistent manner we were able to obtain a more representative picture, and a better fit is found using an exponential equation. This model is consistent with the hypothesis that plaque growth is higher at sites where the artery wall is exposed to oscillatory and low means wall shear stress. The proposed model is preliminary in that several other aspects (like age, and smooth muscle growth kinetics) that influence intimal thickness need to be included. However, this model lends itself for use in computational simulations of blood flow which aim to track plaque growth and their effect on flow in a simple manner. An interesting feature of the data is the separate spread for abdominal aorta and coronary artery. Researchers agree that endothelial cells do respond to shear stress in a particular direction [2], and that intimal thickening is indeed correlated with disturbed flow and low wall shear stress [8]. However, the data suggests that wall shear stress alone may not be the only mechanical variable affecting thickening, and that a correlation will probably have to find a way of accounting for changes in flow direction at a site as well. With the data we selected this is out of the question because the information is not provided, but future experiments may consider reporting such information as well.

ACKNOWLEDGMENTS

Dr. Sarath Duvvuri and Dr. N Nanda Kumar express their sincere gratitude to Dr. Mohan Anand, Associate Professor, Department of Chemical Engineering, Indian Institute of Technology Hyderabad for his valuable suggestions and discussions for successful completion of this research work. As an extension, the authors gratefully acknowledge the Sri Vishnu Educational Society for the continuous moral & financial support to complete this research manuscript.

REFERENCES

1. Bonert M, Leask RL, Butany J, Ethier CR, Myers JG, Johnston KW, Ojha M, "The relationship between wall shear stress distributions and intimal thickening in the human abdominal aorta," Biomed Eng Online, 2:18, 2003
2. Chien. S, "Mechanotransduction and endothelial cell homeostasis: the wisdom of the cell," American journal of physiology, 293(3):H1209-H1224, March 2007.
3. Friedman, M. H, "A Biologically Plausible Model of Thickening of Arterial Intima under Shear," Atherosclerosis, 9(4):511-522, 1989.
4. Friedman, M. H., Hutchins, G. M., Bargeron, C. B., Deters, O. J., and Mark, F. F, "Correlation Between Intimal Thickness and Fluid Shear in Human Arteries," Atherosclerosis, 39:425-436, 1981.
5. Friedman, M. H., Deters, O. J., Bargeron, C. B., Hutchins, G. M., and Mark, F. F, Shear-Dependent Thickening of the Human Arterial Intima, Atherosclerosis, 60(2):161-171, May 1986.
6. Friedman, M. H., Bargeron, C. B., Deters, O. J., Hutchins, G. M., and Mark, F. F, Correlation between wall shear and intimal thickness at a coronary artery branch, 68:27-33, 1987.
7. Gibson CM, Diaz L, Kandarpa K, Sacks FM, Pasternak RC, Sandor T, Feldman C, Stone PH, "Relation of vessel wall shear stress to atherosclerosis progression in human coronary arteries," Arterioscler Thrombosis, and Vascular Biology. 1993 Feb: 13(2):310-315, 1993.
8. Gimbrone, M. A, Vascular Endothelium, "Hemodynamic Forces, and Atherogenesis," The American Journal of Pathology, 155(1):1-5, July 1999.
9. Hayashi, K., Yanai, Y., and Naiki, T. A 3D-LDA study of the relation between wall shear stress and intimal thickness in a human aortic bifurcation. Journal of Biomechanical Engineering, 1:3-9, 1996.
10. Md. Asif Ikbal, "Viscoelastic blood flow through arterial stenosis—Effect of variable viscosity," International Journal of Non-Linear Mechanics, Volume 47, Issue 8, 2012, Pages 888-894, 2012
11. Kane JP, Malloy MJ, Ports TA, Phillips NR, Diehl JC, Havel RJ, "Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens," JAMA: The Journal of the American Medical Association, 264 (23):3007-3012, 1990.
12. Malek AM, Alper SL, Izumo S, "Hemodynamic shear stress and its role in atherosclerosis, JAMA: The Journal of the American Medical Association," 282(21):2035-2042, 1999.
13. N. Nandakumar, Kirti Chandra Sahu, M. Anand, "Pulsatile flow of a shear-thinning model for blood through a two-dimensional stenosed channel," European Journal of Mechanics - B/Fluids, Volume 49, Part A, 2015, Pages 29-35, 2015.
14. Sarifuddin, S. C. and Mandal, P. K, Effect of Asymmetry and Roughness of Stenosis on non-Newtonian Flow Past an Arterial Segment," International Journal of Computational Methods, 6(3):361-388, 2009.
15. Zarins, C. Giddens, D. P., Bharadvaj, B. K., Sottiurai, V. S., Mabon, R. F., and Glagov. S, "Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress," Circulation Research, 53(4):502-514, October 1983.
16. Sajjan MC, Krishna RG. Lip-support prosthesis--a unique approach in management of bilateral facial palsy. Quintessence Int. 2007 Sep: 38(8): 517-520.
17. Suresh Sajjan, M. C, "A simple attachment to the surveyor for effective transfer of path of insertion from diagnostic cast to the working cast," The Journal of Indian Prosthodontic Society 6(2): 72-74, April–June 2006.