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The Impact of Vein Mechanical Compliance on Arteriovenous Fistula Outcomes

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Abstract

Purpose: Arteriovenous fistulae (AVF) are the preferred access for haemodialysis but suffer a high early failure rate. The aim of this study was to determine how venous distensibility, as measured in vitro, relates to early outcomes of AVF formed with the sampled vein.

Methods: Ethical approval was obtained for all aspects of this study. During arteriovenous fistula formation a circumferential segment of the target vein was sampled. Mechanical stress testing of the venous segments was undertaken utilising a dynamic mechanical analyser, with progressive stress loading at 2 N per minute to a maximum of 10 N or until sample disruption. Stress strain curves were obtained for vein samples and Young's modulus(YM) calculated. Duplex assessment of the fistulae was undertaken at 30 days.

Results: 30 patients consented to participate with 29 samples obtained for analysis. Statistical comparison of YM demonstrated no relationship with common cardiovascular risk factors or dialysis status. Subject age greater than 65 was the only patient factor which showed a significant difference in YM ($p=0.05$). Furthermore a negative correlation was confirmed between age and YM (Pearson's $r=-0.465$, [$p<0.05$]). 9 of the 29 subjects suffered an early AVF failure. Mann-Whitney U testing for differences in distribution reported that YM was significantly higher in those fistulas which failed ($p<0.005$).

Conclusion: Reduced venous compliance appears to result in higher failure rates of arteriovenous fistulae. With the advancement of clinical tools such as speckle tracing ultrasound identification of vessel compliance in vivo may produce valuable additional information for clinicians planning AVF surgery.

Introduction

Upper limb autologous arteriovenous Fistulae (AVF) are the preferred vascular access method for chronic haemodialysis[1]. Despite significant advantages over alternative methods, AVF suffer particular problems such as failure to mature and early thrombosis. "Failure to mature" describes insufficient flow within or dilatation of the venous segment of an AVF to allow use for dialysis despite the AVF remaining patent. Failure to mature has been reported in up to 10% of newly formed AVF [2] and as maturation relies upon increasing venous diameter the distensibility of veins has previously been investigated as a potential predictor of AVF success. The aim of this study was to determine how venous distensibility, as measured in vitro, related to outcomes of early failure or failure to mature in AVF formed with the sampled vein.

Materials and Methods

Research Ethics Committee approval was obtained prior to study commencement and informed consent was obtained from each subject. Thirty consecutive, consenting patients undergoing AVF formation were assessed by physical examination and duplex ultrasound (DUS) to determine the optimal site of AVF formation. At operation a distal section of vein was sampled as a complete circumferential segment for testing. Samples were then snap frozen to -80˚ centigrade for storage and transport. Freezing of samples was necessary due to logistical factors and no comparisons were possible between fresh and frozen samples to determine what effect storage of samples might have on results obtained.

The mechanical testing of vein samples was undertaken using the Dynamic Mechanical Analyser (DMA) Q800 (TA Instruments, Delaware, USA). A short section of vein was mounted on the test equipment using a bespoke jig manufactured specifically for this series of measurements (Figure 1). The controlled force/strain rate mode of the analyser was used with a preload of 0.25 Newtons (N) applied to all samples to remove slack prior to commencing testing. A progressive stress loading at 2 N per minute to a maximum of 10 N or until sample disruption was used.

Since the primary focus of the study was vein compliance in relation to early failure or failure to mature follow up was limited to the 30 day post operative period. Participants were assessed at 30 days (+/- 3 days) post surgery both clinically and with DUS to record the diameter of the AVF draining vein as well as an estimations of AVF flow based upon peak systolic velocity and end diastolic velocity. Failure to mature was defined as a fistula which remained patent but had with a blood flow of <250ml/min at 30 days[3].

Calculating Young's Modulus

Hooke's law states that the stress applied to a material is proportional to the strain on that material. In a plot of stress versus strain is therefore a region of constant slope during which Hooke's law holds. The gradient of the curve at this point represents the Young's modulus for the material (the ratio of stress over strain for a material). Young's modulus is the recognised measure of the ease of deformation of an elastic material. A high value for Young's Modulus implies an inelastic or stiff material whilst a low value suggests a very flexible material.

Biological materials do not show the same linear stress-strain curves as engineering materials. Biological materials consisting of mixed fibres will instead tend to exhibit non-linear, anisotropic behaviour resulting in a stress strain curve which is typically lazy-S shaped with 3 distinct regions as demonstrated in Figure 2.

For accurate estimation of Young's modulus, region 2 in which Hooke's law holds was utilised for measurement of compliance in the tested vessels. However, estimates of Young's modulus were also made in region 1 as this might allow better comparison with published data for veins tested for compliance under lower loads as would be expected under tourniquet testing.

Output data was plotted into stress strain curves using Microsoft Excel. The gradient was calculated for both the initial loading in "Region 1" and also in "Region 2" of the curve where a true linear relationship was seen and in which Hooke's Law holds.

Statistical Analysis

Chi-square tests were undertaken for categorical data and t-tests or Mann Whitney U tests for interval data/ordinal, depending on normality of the data and type of data. All statistical analyses were undertaken on SPSS 19. A p-value of <0.05 was considered to indicate statistical significance.

Results

One sample proved inadequate for mechanical testing hence results for 29 samples are reported. The average age of subjects was 63 years (34-83) and 23 male (79%). 21 samples were from cephalic vein used in Snuff-Box or radio-cephalic fistulae in the distal arm, 7 from cephalic vein used in brachio-cephalic in the anticubital fossa and 1 from a basilic vein which was transposed in the subject's upper arm. Summary data for study subjects is shown in Table 1.

Compliance

On analysis of the stress strain curves two samples ruptured before an obvious yield region and as such resulted in a J shaped curve of region 1 and 2 only whilst the majority of samples demonstrated the expected lazy S curve. Young's modulus in region 2 for the cohort of samples tested returned a mean of 0.136 MPa and median of 0.122 MPa. Results had an inter quartile range of 0.1680 MPa and a total range between 0.0064 MPa and 0.3564 MPa.

Estimation of Young's modulus in region 1 returned a mean value of 0.0164 MPa and a median of 0.0079 MPa. Results had an inter quartile range of 0.0160 MPa and a total range between 0.0001 MPa and 0.0777 MPa.

Young's Modulus in region 2 was compared between those groups of subjects with and without the presence of factors which were predicted to potentially have an effect on venous compliance including gender, diabetes, hypertension, smoking and dialysis status at time of surgery. Those receiving forearm AVF were also compared to those receiving upper arm AVF. The only factor which showed in a significant difference in Young's modulus was if a subjects age was greater than 65 ($p=0.05$ – Mann Whitney U testing).

Further exploration of the relationship between Young's modulus and age revealed a significant negative correlation between Young's modulus and age (Pearson's $r=-0.465$, $p<0.05$. Figure 3)

Compliance with early AVF failure

9 of the 29 subjects (31%) suffered an AVF failure within 30 days, all of which were due to thrombosis in the fistula vein. There were no cases of failure to mature in this series. Median and interquartile range of Young's modulus measured in region 2 in samples from AVF which failed was 0.2159 MPa and 0.1279 MPa compared to 0.0744 MPa and 0.1233 MPa respectively in samples from AVF which remained patent. Mann-Whitney U testing for differences in distribution reported a significant difference between Young's modulus in region 2 in the two groups ($p<0.005$).

Estimated Young's modulus (region 1)

Young's Modulus in region 1 was also compared between those groups of subjects with and without the presence of factors discussed above but was not significantly different between groups of subjects with or without any of these factors. Median and interquartile range of Young's modulus measured in region 1 in samples from AVF which failed was 0.0157 MPa and 0.0606 MPa compared to 0.007 MPa and 0.0111 MPa in samples from AVF which remained patent. Mann-Whitney U testing for differences in distribution reported no significant difference between Young's modulus in region 1 in the two groups ($p=0.085$). Though the low p value suggests a trend towards poorer compliance as measured in region 1 and AVF failure.

Discussion

This series has demonstrated a significant increase in directly measured vein wall stiffness in AVF which suffered early failure . Previous clinical data supports this finding such as data that the average tourniquet application increase in venous diameter in veins used for AVF formation was only 12% in those which subsequently failed, compared to 48% in veins utilised to create patent AVF [4]. Strain-gauge plethysmography in uraemic patients has also demonstrated that where venous distensibility was <0.50 mL/mmHG 100% of subsequent AVF failed where as when venous distensibility was >0.50 mL/mmHg only 20% failed[5]. Poor venous distensibility may also be a contributing factor in the 15 - 40% of AVF that may be expected to thrombose in the early post operative period[6 7] (i.e. primary failure) as inadequate distension would result in reduced flow through the anastomosis and potentiate risk of thrombosis at the site of intimal injury.

The underlying reasons for differences in venous compliance between patients has previously been investigated in studies of arterialised venous conduits as used in coronary and lower limb bypass grafting. These consistently report the presence of pre-existing disease altering venous wall structure which can affect patency and contribute to the development of later stenosis in both coronary and femoro-distal bypass conduits [8-11]. Wali et al studied the pre-existing morphological changes in the wall of the cephalic vein before AVF construction and compared this to vein from non uraemic upper limb vein samples [12]. Compared with normal cephalic veins, all pre-access cephalic veins showed generalized intimal hyperplasia. Veins from uraemic patients demonstrated loss of internal elastic lamina and endothelial cell layer, mucoid or myxoid degeneration, inflammatory cell infiltration and mural calcification. This suggests that macroscopically normal cephalic veins used in AVF construction are highly likely to have morphological abnormalities which could adversely affect the outcome of AVF surgery. When histological appearances of common and external iliac vein samples collected from patients receiving renal transplantation were compared to inferior cava and common iliac vein from healthy donors and cadavers, the uraemic veins demonstrated a significant increase in the thickness of the venous media in hypertensive uraemic patients as compared to normotensive uraemic patients and controls[13]. This would appear to suggest that the cardiovascular risks factors associated with arteriosclerosis may have similar effects on the venous circuit and the potential quality of vein used in access grafts.

The results of this study demonstrated a significant negative correlation between advancing age and Young's modulus in region 2 (p=0.05). This appears contrary to the generally accepted view of increasing vessel stiffness with increasing age. However the majority of reported data relates to the arterial vessels and increasing stiffness is believed to be due to a decline in the relative concentration of elastin fibres compared to collagen fibres [14]. This decline in the elastin fibres leads to vessel ectasia and relative stiffness as the stress loading of the arterial wall is taken up by inelastic collagen fibres rather than deformable elastin fibres. In effect the stress-strain plot commences within region 2 rather than region 1 of the lazy s curve. Since collagen is far stiffer than elastin this results in less complaint arterial vessel walls with advancing age. The authors are aware of only one other series reporting venous compliance in relation to age which showed an inverse relationship between age and vein compliance during in vivo testing in healthy volunteers [15]. The explanation for this difference on outcomes is unclear however the simplistic explanation of the degradation of elastin and increased relative concentration to collagen may not be a complete reflection of the structural changes occurring in vessel walls. Catell et al. documented a significant loss of both vessel wall dry weight and mass of collagen and elastin with age. However, the concentration of these fibres in the vessel wall was actually increased with increasing age. This finding would suggest that there was a significant loss of other vessel wall components at a rate which exceeds that at which collagen and elastin are lost.[16]. Furthermore, Fonseca et al. studying vein samples reported that increases in age resulted in decreases in larger collagen fibres, whilst no significant changes in small collagen fibres were found [17].

This study is limited in that it was performed on in vitro specimens that had been harvested and frozen prior to testing. As such the testing performed was a measurement of underlying structural compliance of the vein tissue and may thus be quite different to the physiological compliance of the vein in situ in vivo. It may therefore be the case that this study has shown results of compliance changes with age that actually reflects the reduced supporting tissues in the vessel wall or altered collagen makeup of the vessel wall. It may be that in vivo studies may show increased stiffness with increasing age by measuring the mechanical effects of supporting connective tissues or basal smooth muscle tone rather than simply the vessel wall structural compliance as in this study.

Of note the rate of failure in female subjects and in those receiving an ACE inhibitor was double that in males or those not prescribed ACE inhibition. Females are known to suffer failure more commonly than males[18] and prescription of ACE inhibition may reflect a higher cardiovascular risk profile. This small study is not powered to explore this finding in any detail.

The clinical relevance of the results reported here is that any bedside or non invasive test of venous compliance which could be performed prior to AVF formation may have significant bearing on the site chosen or the management of the subsequent AVF. Tests available are limited at present in most units but simple bedside measurement of percentage change in vein diameter with and without tourniquet application has shown promise in predicting AVF Patency[4]. However, distension under tourniquet likely represents stresses as might be expected in region 1 of the stress strain curve with relatively low venous pressures. As a vein is utilised in an AVF, higher stress loading of the vessel wall would be expected due to arterial pressures applying radial loading to the vessel. More accurate estimations of vein compliance could be achieved using using strain-gauge plethysmography[5] but this technique is complex to perform and remains in the realm of research laboratories at present.

Elastography and ultrasound speckle tracing is a recently developed technique utilising high frequency ultrasound to apply mechanical compression or vibration to tissue and then detect the extent of resultant deformation. By utilising simplifying assumptions, the deformation can then be interpreted as representative of the underlying Young's modulus or compliance of the tissue. Early studies utilising these techniques in assessing vein compliance in the forearm suggest it may provide detailed, high-resolution and spatially accurate maps of vein-wall mechanics [19]. Assessment of stenoses in AVF draining veins with elastography reported lower values of strain in stenotic regions compared to the remainder of the vessel, indicating greater stiffness of the vessel wall at these points [20]. The non invasive ultrasound speckle tracking techniques described in these papers has clear potential to determine vein wall mechanical properties noninvasively, and may in the future become an adjunct to AVF planning.

Conclusion

The histological basis for changes in compliance both with age and between subjects warrants further investigation. With the advancement of clinical tools such as speckle tracing ultrasound identification of vessel compliance in vivo may produce valuable additional information for clinicians planning AVF surgery.

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Variable	Failures with variable present	Failures with variable absent	Young's Modulus with variable present			Young's Modulus with variable absent			Difference
			n=	Median	IQR	n=	Median	IQR	Signif (p=)
Age >65	2/ 15 (13%)	7/ 14 (50%)	15	**0.0907**	*0.1304*	14	**0.1756**	*0.1458*	**>0.05**
Male gender	6/23 (26 %)	3/6 (50 %)	23	**0.0734**	*0.2369*	6	**0.1455**	*0.1597*	**0.896**
Diabetes	2/10 (20%)	7/19 (36%)	10	**0.1391**	*0.1168*	19	**0.0918**	*0.1927*	**0.429**
Hypertension	3/ 13 (23%)	6/ 16 (37%)	13	**0.0918**	*0.1674*	16	**0.1467**	*0.1885*	**0.449**
Smoking	4/ 12 (33%)	5/ 17 (29%)	12	**0.1339**	*0.1190*	17	**0.1131**	*0.1941*	**0.879**
ACEi	2/ 4 (50%)	7/ 25 (28%)	4	**0.0909**	*0.1572*	25	**0.1455**	*0.1752*	**0.444**
Statin	3/ 11 (27 %)	6/ 18 (33%)	11	**0.091**	*0.1905*	18	**0.1467**	*0.1655*	**0.492**
On Dialysis	5/ 16 (31%)	4/ 13 (30%)	16	**0.1024**	*0.1191*	13	**0.1904**	*0.1737*	**0.374**

Table 1 -Comparison of Young's modulus with and without various factors (n- number, SD, standard deviation, ACEi – Angiotensin converting enzyme inhibitors)

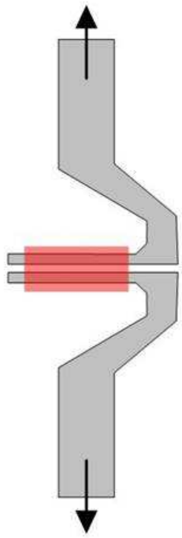

Figure 1 - Jig for mechanical deformation testing of vein samples – the red section shows the testing position of the specimen of vein with the pins of the clamps both passing through the vein lumen.

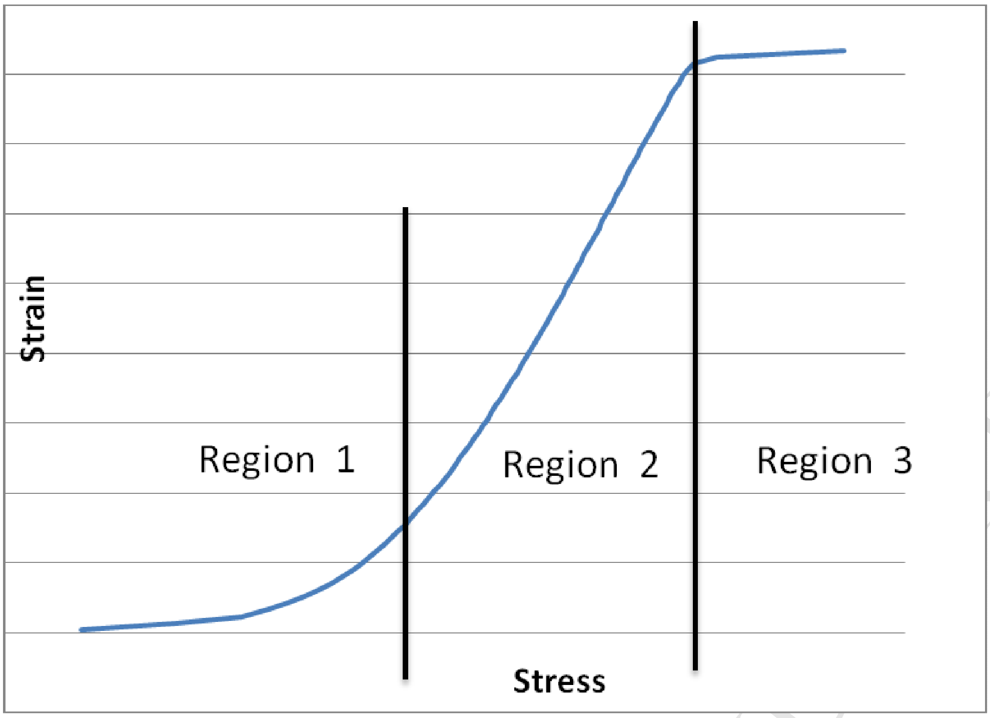

Figure 2 – Typical stress-strain curve for soft tissues under increasing loads showing 3 distinct regions of response

Region 1 - Mainly accounts for stretch of the interlaced elastin fibres, and in this region the collagen fibres are not yet aligned with the load and remain largely unaffected [19].

Region 2 – As further loading occurs, elastin fibres are fully aligned and collagen fibres are now in the direction of the force and begin to be bear load. In this region the tissue exhibits a near linear stress-strain relationship and this represents the mechanical elastic modulus or young's modulus of the tissue [19].

Region 3 – At high loads the Collagen fibres reach full stretch and strongly resist further deformation causing the tissue to behave in a very stiff manner. This is the "yield" region and as load increases, the structure of the tissue begins to permanently alter as collagen fibres start to break [19].

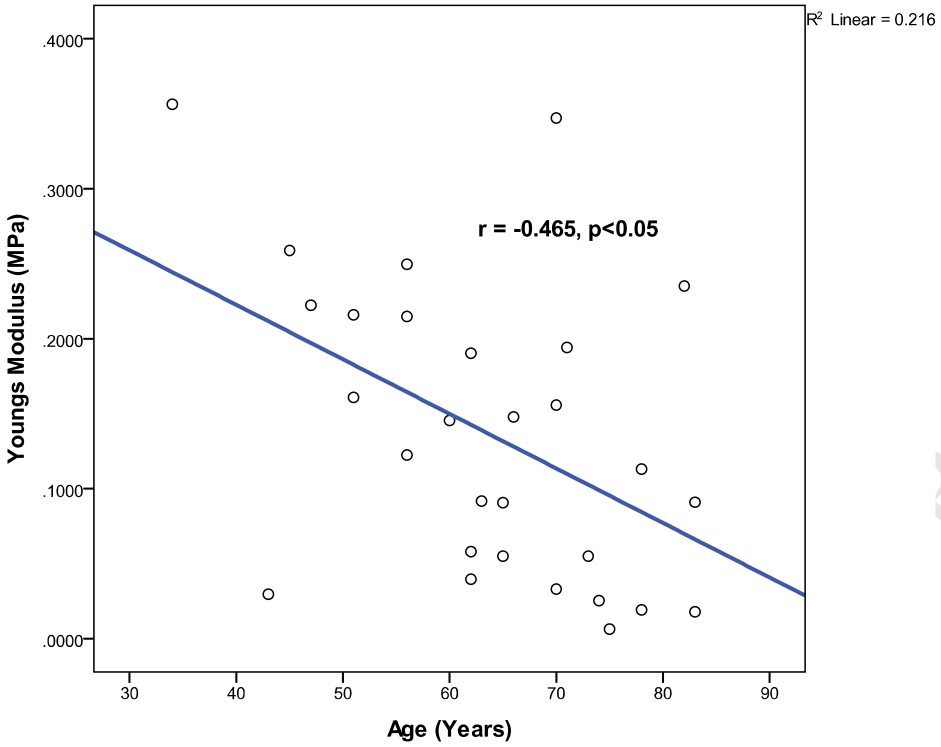

Figure 3 - Young's Modulus plotted against subjects age (line of best fit indicates significant negative correlation) (P value shown calculated using Pearson's test for correlation)