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Modelling the growth of popliteal artery aneurysms

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Abstract

Background: Popliteal artery aneurysms (PAA) comprise up to 85% of all peripheral aneurysms. However, few longitudinal studies track the progression of PAA size, which is the determinant of intervention. This study aims to track the progression of asymptomatic

PAA in a hospital based lower limb ultrasound service and compare models of aneurysm growth that best fit our patient cohort

Methods: A retrospective single-centre cohort study that included patients who had a PAA on arterial duplex ultrasound of the lower limbs between the 1st January 2011 and 1st of January 2016. Progression of PAA size and progression to event or intervention were the primary outcome measures.

Results: 3217 records were screened with 282 images analysed. 47 limbs with PAA were identified in 32 patients (9 had bilateral PAA) and 20 had an associated AAA. Linear multi-level modelling (MLM) was used to estimate PAA growth at 2.4 mm/year (95% CI: 1.6-3.7). The growth was estimated at 0.8 mm/year (95% CI: 0.1 - 1.5) in those without an AAA and 3.5 mm/year (95% CI: 2.9 - 4.2) in those with a known AAA (previous open repair, previous EVAR or AAA under surveillance). The difference was statistically significant ($p < 0.001$).

Conclusions: Growth rates of PAA were heterogeneous and linear MLM is a statistical technique presented that best predicted its growth. Our data raise the possibility that patients with PAA and an existing AAA have faster PAA progression than those without AAA. However, this link required further dedicated study.**Introduction**

A popliteal artery aneurysm (PAA) is a focal dilatation and weakening of the popliteal artery. PAA is the most frequently occurring peripheral aneurysm, accounting for 85% of all such aneurysms (1). They are followed in frequency by femoral artery aneurysms, and together these constitute 90% of all peripheral aneurysms (2).

The majority of PAA are degenerative in nature. Men outnumber women accounting for more than 90% of the population cohort, greater than 50% are bilateral, and over a third of those with a PAA have a coexistent aortic aneurysm (3). PAA are typically asymptomatic, although, when symptomatic, they typically present with lower extremity ischemia from acute or chronic thrombosis, distal embolization, or, rarely, rupture (4)

Symptomatic PAA's of any size are treated, either by surgical ligation combined with autologous vein bypass via a medial approach (5, 6), or by endo-prosthesis (7). While surgical treatment is usually preferred in an emergency (8), the evidence on first line treatment in a non-emergency setting is unclear.

The main determinant of asymptomatic repair, however, is PAA size. Whilst some studies recommend that asymptomatic aneurysms larger than 20mm are treated (9), other centres successfully conservatively manage PAAs between 20-30mm with no evidence of thrombosis in this group (10) and only recommend treating asymptomatic aneurysms larger than 30mm (11). Regardless, it is clear that with increasing size, the risk of PAAs becoming symptomatic increases leading to limb-threatening scenarios (10).

Whilst the results of these studies have helped to inform us of the size at which intervention should ideally be performed, little work has been done investigating the progression of PAA. This is in contrast to AAA, where a significant body of work has been conducted to investigate the rate of growth (12, 13). From our understanding of AAA progression, growth depends on size (13), which needs to be accounted for in a non-linear model (simple growth/time analysis or linear regression).

One previous study has attempted to study and model the expansion rates of asymptomatic PAA (14). Unfortunately, the value of the study is limited as it does not account for the lack of independence in observations (i.e. sequential measurements in the same patient).

In this study, the progression of asymptomatic PAA in a single UK tertiary vascular centre is tracked over a five-year period and compare the use of simple growth/time analysis, linear regression and linear multilevel modelling (MLM) to model PAA growth.

Methods

Retrospective patient data was collected from a regional vascular unit serving a local population of >1 million patients in the northern United Kingdom. Patients were identified from arterial duplex scans performed between the 1st January 2011 and 1st of January 2016. The inclusion criteria were any patient who had a PAA on arterial duplex ultrasound (USS) of the lower limbs and had 2 or more USS scans per limb. A PAA was defined as a popliteal artery with a diameter >10mm. The exclusion criteria were any patients that had previous surgery or endovascular treatment for a popliteal artery aneurysm. All imaging data from the index scan until limb intervention or the 1st of January 2017 was included. If previous imaging of the lower limb was done before PAA diagnosis, data from this was also included.

Patients were imaged in a relaxed lateral decubitus position. Using an IU22 ultrasound scanner [Philips Healthcare Systems, Amsterdam, Netherlands]. The arterial inflow was assessed initially for patency starting caudal to the adductor hiatus with the distal SFA

through to the distal TPT in the popliteal fossa. A combination of Ultrasound B-Mode, Color and Doppler velocity assessment measurements were taken. Vessel sizing assessment measured the outer boundary wall to outer boundary wall specifically across the widest segment of popliteal artery. Measurements were taken in both transverse and longitudinal images with comparison to previous imaging available for reference in line with departmental protocol. Scanning intervals were arranged by the clinician in charge of the patient's care. All ultrasound imaging was performed by post-graduate, state registered sonographers with autonomy for their independent practice and regular departmental audit for quality assurance.

Clinical data on the included patients was gathered from the hospital electronic medical records system (Patient Pathway Manager, PPM+). The primary outcome measured was the progression of PAA size and the secondary outcome was progression to event or intervention.

Three statistical growth models were applied to the data; simple growth/time analysis, linear regression model and linear multilevel modelling (MLM). Statistical analysis was performed using the R-environment by a specialist biostatistician (PB).

Growth/time analysis was performed by calculating the difference between the first and last popliteal artery aneurysm diameters and dividing this between the length of time between the measurements. A linear regression model was fitted with popliteal artery diameter as the response element and time from the initial scan as the predictor. A parametric, linear multilevel model with two levels and measurements nested within patients was fitted by full

maximum likelihood, with popliteal artery diameter as the response element and time from the initial scan as the fixed predictor. A random, normally distributed intercept term and a random, normally distributed slope term were added for each patient.

Model comparisons were made using the Akaike Information Criterion (AIC) for the purposes of goodness-of-fit analysis. The AIC does not give us information about the quality of the model itself per say, but allows us to compare and determine which model better represents the patient data. AIC rewards goodness of fit and the preferred model has the lower AIC value.

This study has been approved by the NRES East of England - Cambridge Central Research Ethics Committee (REC Ref: 17/EE/0326).

Results

3,217 records were screened in a hospital based lower limb ultrasound service and a total of 47 limbs with PAA were identified in a cohort of 32 patients (15 patients, 46.9%, had bilateral PAA). There were 29 men and 3 women. The mean (SD) age was 74.6 (8.3) years. The mean (SD) length of surveillance was 3.71 years (2.59) with 174.2 cumulative years of data collected. The mean (SD) diameter of PAA at diagnosis was 16.0 mm (7.1). Eleven patients (23.4%) had detectable thrombus within the artery on diagnosis. The comorbidities are described in Table 1 and the AAA status is described in Table 2.

Of the 47 with a PAA, 1 acutely thrombosed (this was managed conservatively) and 10 (21.3%) eventually proceeded to intervention of which 2 were emergency surgical repair.

The mean (SD) time to event (thrombosis or repair) duration was 2.05 years (2.1). The mean size at event (thrombosis or repair) was 29.5 mm (9.1).

A total of 282 ultrasound images were analysed and used in the analysis of popliteal artery aneurysm growth and growth estimates were created for the popliteal aneurysm cohort using 3 different modelling techniques. In the simple growth/time model, popliteal artery aneurysm growth was estimated at 11.7 mm/year (95% CI: 3.0 – 20.4 mm). In the linear regression model, popliteal artery aneurysm growth was estimated at 0.47 mm/year (95% CI: 0.14 – 0.81 mm). A plot of the linear regression model of popliteal artery aneurysm growth is shown in Figure 1. In the linear multi-level model, popliteal artery aneurysm growth was estimated at 2.4 mm/year (95% CI: 1.6 – 3.7 mm). Example individual patient trajectories using the linear multilevel model of popliteal artery aneurysm growth is shown in Figure 2. A comparison plot of the growth estimates including; growth/time model, linear regression model and linear multi-level model is shown in Figure 3.

The AIC cannot be calculated for the growth/time model. For the linear regression model, the AIC was 907.9 and for the linear multi-level model the AIC was 79.8.

A combined linear multi-level model was used to estimate the growth for the patients with known AAA and those without. The growth was estimated at 0.8 mm/year (95% CI: 0.1 – 1.5) in those without a AAA and 3.5 mm/year (95% CI: 2.9 – 4.2) in those with a known AAA (previous open repair, previous EVAR or AAA under surveillance). This was statistically significant ($p < 0.001$) and the comparison plot of growth estimates using the presence of an

AAA as a covariate is shown in Figure 4. A full description of the model definition and results can be found in Appendix 1.

Discussion

In this study, popliteal artery aneurysm growth is modeled in a cohort of 47 limbs with a popliteal artery aneurysm before intervention and three different statistical modelling approaches are compared. Concepts applied here have been previously applied to abdominal aortic aneurysm (AAA) modelling (13). The growth model estimates are plotted (with 95% Confidence intervals) in Figure 1.

The growth/time model produced an over-estimate of growth compared to the other models. This is likely due to the fact that the final scan triggered the intervention (surgical or endovascular repair). This model also ignored a majority of the data points as only 94 of the total 282 observations were utilized. AIC is not applicable for this method and cannot be calculated.

The linear regression model underestimated growth compared to the linear multilevel model. Due to the heterogeneity of individual growth trajectories, the measurements, when pooled, appear to reduce any visible effect of growth as shown in Figure 2. However, as this model does not take into account the multi-level structure of the data, it is an inaccurate model to use.

In the linear multi-level model (MLM), linear regression is modeled for each individual patient before they are combined to provide an overall growth estimate and gives a higher growth estimate than the linear regression model. Example trajectories of individual patients are shown in Figure 3.

The AIC is improved in the MLM with an AIC = 79.8 in the MLM compared to an AIC = 907.9 in the linear regression model which suggests that the MLM better represents the data. Using this linear MLM modelling technique the growth rate of PAA in our cohort was 2.4mm/yr. This is not dissimilar to previous estimates of AAA growth from our own centre (13) or the RESCAN collaboration (12) (in which data from our centre was also included).

The MLM was applied using the presence of an AAA as a covariate. There is a small difference between the growth estimate of the two groups with those with an existing AAA (n=20) exhibiting faster growth than those with a confirmed normal abdominal aorta (n=12). The link between the presence of an AAA and faster PAA progression does require further dedicated study. Nevertheless, our study stresses the importance of identifying patients with a concomitant AAA in order to plan more regular surveillance.

Due to the heterogeneous nature of PAA growth, surveillance intervals need to be tailored to individual patients based on their portfolio of risk factors. This model takes us a step further in developing a risk stratification tool to determine a safe surveillance interval based on aneurysm growth rate and patient factors including gender, smoking status and diabetes which are known to influence aneurysm growth (12, 15). Further studies may also utilize

pro-aneurysmal biomarkers (i.e. MMP-9, TIMP-1, α1-Antitrypsin) in understanding the underlying pathogenesis and a potential target for drug activity (16).

Limitations

This study has several limitations. There was likely a degree of intra-operator variability as the measurements were performed by several operators for the same patient. The precision of the measurements was also likely affected with the small millimeter measurements of the popliteal artery. The patient cohort was selected from a single centre, which affects the generalizability of our findings.

The overall sample size was small which limits our ability to adjust for other covariates including age, gender and comorbidities. Sample size calculation in multi-level models however remain an active area of research and as little as 20 units may be sufficient for statistical inference (17). Due to relatively short mean (SD) follow-up period of 3.71 years (2.59), quadratic modelling, which would adjust for growth dependent on size, could not be performed.

Conclusions

PAA growth is heterogeneous among individuals and shows similarities with AAA growth. Linear MLM better represents the pattern of growth than the other methods tested. PAA growth appears to be enhanced in the context of AAA in our patient cohort however this link requires further dedicated study with the use of large scale cohort studies over a prolonged length of time.

Acknowledgements

MA Bailey and DJA Scott contributed equally to this study.

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Appendix 1

A parametric, linear multilevel model with two levels and measurements nested within patients was fitted by full maximum likelihood, with popliteal artery diameter as the response element and time from the initial scan as the fixed predictor. A random, normally distributed intercept term and a random, normally distributed slope term were added for each patient. The model definition and results are described below.

model.intslp=lme(popliteal.diam2~normal.date2,random=~normal.date2|study.no2,method="ML",data=popliteal)

summary(model.intslp)

Fixed effects: popliteal.diam2 ~ normal.date2

	Value	Std.Error	DF	t-value	p-value
(Intercept)	*1.6623440*	*0.12907442*	*104*	*12.878957*	*0.000*
normal.date2	*0.2445626*	*0.02032221*	*104*	*3.176949*	*0.002*

intervals(model.intslp)

Approximate 95% confidence intervals

Fixed effects:

	lower	est.	upper

(Intercept) 1.40836111 1.66234398 1.9163269

normal.date2 0.16457412 0.24456263 0.3745511

attr(,"label")

Appendix 2

A combined multi-level model was used to estimate the growth for the patients with known AAA and those without. The model definition and results are described below.

model.intslp=lme(popliteal.diam2~normal.date2*aaastatus,random=~normal.date2|study.no2,method="ML",data=popliteal, control = lmeControl(opt = "optim"))

summary(model.intslp)

*Fixed effects: popliteal.diam2 ~ normal.date2 * aaastatus*

	Value	Std.Error	DF	t-value	p-value
(Intercept)	*1.7154834*	*0.16698699*	*194*	*10.273156*	*0.0000*
normal.date2	*0.0813090*	*0.03430201*	*194*	*2.370386*	*0.0188*
aaastatus	*-0.2446424*	*0.21829126*	*44*	*-1.120716*	*0.2685*
normal.date2:aaastatus	*0.2647305*	*0.06386290*	*194*	*3.345208*	*0.0010*

intervals(model.intslp)

Approximate 95% confidence intervals

Fixed effects:

	lower	est.	upper
(Intercept)	*1.38887356*	*1.71548341*	*2.0420932*
normal.date2	*0.01421770*	*0.08130899*	*0.1484003*
aaastatus	*-0.68092855*	*-0.24464241*	*0.1916437*
normal.date2:aaastatus	*0.23093907*	*0.26473052*	*0.3025220*

attr(,"label")