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SAFETY

Mechanical testing of human cardiac tissue: some implications for MRI safety

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Purpose. The effects of aging on tissue strength and its ability to withstand forces associated with MRI have not been investigated. This study aimed to determine the forces required to cause partial or total detachment of a heart valve prosthesis in patients with age-related degenerative diseases exposed to MRI. *Methods*. Eighteen tissue samples excised during routine heart valve replacement surgery were subjected to a suture pull-out test using a tensile materials testing machine. Five preconditioning cycles were applied before commencing the final destructive test. The test was complete when the sample ruptured and the suture was pulled completely free from the tissue. Results were compared with previously calculated magnetically induced forces at 4.7 T. *Results.* All tissue samples displayed a basic failure pattern. Mean forces required to cause initial yield and total rupture were 4.0 N (± 3.3 N) and 4.9 N (± 3.6 N), respectively. Significant factors determining initial yield were stenosed calcific tissue ($p < .01$), calcific degeneration (single pathology) ($p < .04$) and tissue stiffness ($p < .01$). Calcific degeneration ($p < .03$) and tissue stiffness ($p < .03$) were also significant in determining maximum force required to cause total rupture. *Conclusion*. Specific age-related degenerative cardiac diseases stiffen and strengthen tissue resulting in significant forces being required to pull a suture through valve annulus tissue. These forces are significantly greater than magnetically induced $\leq$ 4.7 T. Therefore, patients with degenerative valvular diseases are unlikely to be at risk of valve dehiscence during exposure to static magnetic field $\leq$ 4.7 T.

Key Words: Magnetic resonance imaging; Heart valve replacement; Tensile strength; Suture pull-out test

1. Introduction

Improved longevity has resulted in significant changes in the age profile of many populations (1, 2) and a rise in the prevalence of age-related diseases (3–5). Normal aging leads to decreases in bone mass and muscle strength as well as decreased immune responses to infections. As a result, tissue strength and flexibility are weakened. It is estimated the body reaches peak efficiency at aged 30 and then declines. For example, the average rate of tensile strength of muscle in the cardiovascular system decreases by 7% in the 30–39 year olds and 21% in the 60–70 year olds (i.e., standard is 0.11 Mpa) (6, 7). Therefore, the heart muscle of an 80 year old could be expected to be functioning at only two-thirds its peak strength as a result of aging. Clinicians should therefore consider the effects of age-related diseases on the body's ability to retain an implant in place when exposed to strong magnetic fields, such as those present during MRI.

The majority of MR systems in clinical use today are $\leq$ 1.5 T. However, MR systems with field strengths $\geq$ 1.5 T are becoming more common in research and clinical institutions worldwide (8–11). Although studies have been conducted to evaluate the safe exposure of implant patients to MRI (8–17), to our knowledge, no studies have been conducted to assess the safe exposure of elderly implant patients and those who have suffered a past or current episode of infection involving the implant site to MRI. This study tested the strength of human cardiac valve annulus tissue ex vivo in order to determine the forces required to cause partial or total detachment of a heart valve from the surrounding tissue, i.e., valve dehiscence. The results were then compared with previously calculated magnetic forces to determine whether these would be sufficient to cause valve dehiscence (14, 15).

2. Methods

Tissue was excised from the annular ring of fibrous tissue around the native valve of 18 patients (13 women and 5 men

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aged 29–89; mean age 66 ± 14 years) who had undergone first-time elective heart valve replacement surgery at a single cardiac centre in the United Kingdom and had consented for tissue to be used in the study. Aortic valve replacement (AVR) occurred in 13 patients, and mitral valve replacement (MVR) in 5 patients. Seven patients were diagnosed with aortic stenosis (AS), 5 patients had mixed valve disease (MVD),[a] 4 patients had calcific degeneration (CD),[b] and the remaining 2 patients had a diagnosis of infective endocarditis (IE). None of the patients had undergone pre-operative diagnostic MRI to assess cardiac pathology.

All tissue samples were immediately preserved in Hartmann's solution for a period of between zero to 14 days and kept in cold storage at − 8°C. This method of preservation protected the tissue samples from deterioration and the rigours of freeze/thaw preservation methods, which can compromise the tensile qualities of tissue. A standardized procedure used to assess the strength of human and animal tissue used in the manufacture of heart valve prosthesis, known as the suture pull-out strength test, was modified for the purposes of this study (18). Each tissue sample was cut into a 10 mm × 10 mm strip, and a suture was placed 3 mm from one end using 2.0 prolene. A 5 mm loop was then created, placed onto a spike and secured in a clamp and mounted in a 1445 Materials Testing Machine (Zwick Limited, Ulm, Germany), (Fig. 1a and 1b). The free end of the tissue sample was secured in the lower part of the clamp, and liquid CO_2 was blown through the clamps so that there was enough refrigeration to freeze the tissue locally. Two reflective markers of 2 mm diameter were placed on the specimen, one on the suture and the other on the cardiac tissue adjacent to the suture. An infra-red camera on a non-contacting extensometer was aligned with the markers.

Soft tissue, excised and stored, is known to experience stress relaxation and creep (19). It is recognized that prior to any test to assess tensile strength the tissue must undergo load preconditioning until adjacent curves appear to be identical and a reference state is therefore set (20). Studies have shown the number of preconditioning cycles required to reach the reference state in soft tissue varies (20–22). The hysteresis curve resulting from our preconditioning tests, repeated after only a few cycles at 0.6 mm and between 1 and 3 N (Fig. 2), and represented the limit of the 'toe region': a point which will lie well below any yield point. The tissue was therefore preconditioned for five cycles at a displacement rate of 0.6 mm per minute before commencement of the final destructive test. The test was complete when the sample ruptured and the suture was pulled completely free from the tissue.

2.1. *Statistical analysis*

All statistical analysis was performed with Stata 6.0 software (Stata Corporation, College Station, Texas, USA). Regression analysis was conducted to test whether magnetic forces induced during MRI (at 4.7 T) are sufficient to cause valve dehiscence in tissue weakened by age and/or disease. Univariate linear regression analysis was performed to predict outcome measures (i.e., force, yield, stiffness[c]) against age, gender, valve site, and valve pathology (independent variables). Tissue stiffness was also treated as an independent variable and was therefore subjected to univariate regression analysis against force and yield. A p value $< .05$ was considered to be statistically significant. Secondly, a multiple pair-wise correlation coefficient, with a significance level of coefficients of $\geq 5\%$, was performed to establish the closeness of the relationships between the independent variables upon tissue stiffness and yield force.[d]

3. Results

All tissue samples displayed a basic failure pattern. Figure 3 shows the force-displacement response of sutures in human cardiac valve tissue has three regions: an initial toe region when the suture is fully tensioned; a linear region during which the system behaves elastically until the yield point when initial tearing begins; and tearing continues to a maximum force after which, rupture occurs often quite rapidly (failure region). The mean force at which the tissue yielded was 4.0 N ± 3.3 N (mode 3.1 N, range 0.2–14.0 N) and the mean maximum force was 4.9 N ± 3.6 N (mode 3.4 N, range 1.4–14.0 N).

Univariate analysis identified tissue stiffness ($p < .03$) and CD ($p < .01$) as significant factor in determining maximum force required to cause total destruction. Although calcified stenotic tissue[e] had a p value of .06 and was therefore not considered significant in determining maximum destructive force, it was identified as being significant in determining initial yield force ($p < .05$). Two other factors were also identified as significant in determining initial yield force, these were stiffness ($p < .01$) and CD[b] ($p < .04$). The correlation coefficient matrix identified positive correlations

[a]Refers to mixed single valve disease, e.g., mitral valve stenosis and regurgitation, aortic valve calcification and myxomatous degeneration, etc.

[b]Severe calcification was defined as a hardening of the tissue resulting from calcium deposits with a thickness of ≥ 1 mm and/or an inability of the tissue to bend, i.e., the tissue snapped. Mild to moderate calcification was defined as hardening of the tissue and a thickness of < 1 mm with some tissue flexibility, i.e., the tissue could be bent and did not snap.

[c]Stiffness is defined as the slope denoting the stress/strain relationship for a material under uniaxial force.

[d]Yield force refers to the force required cause the tissue to initially tear.

[e]Calcific stenotic tissue refers to a diagnosis of calcification of the tissue which leads to narrowing of the valve annulus (i.e., stenosis).

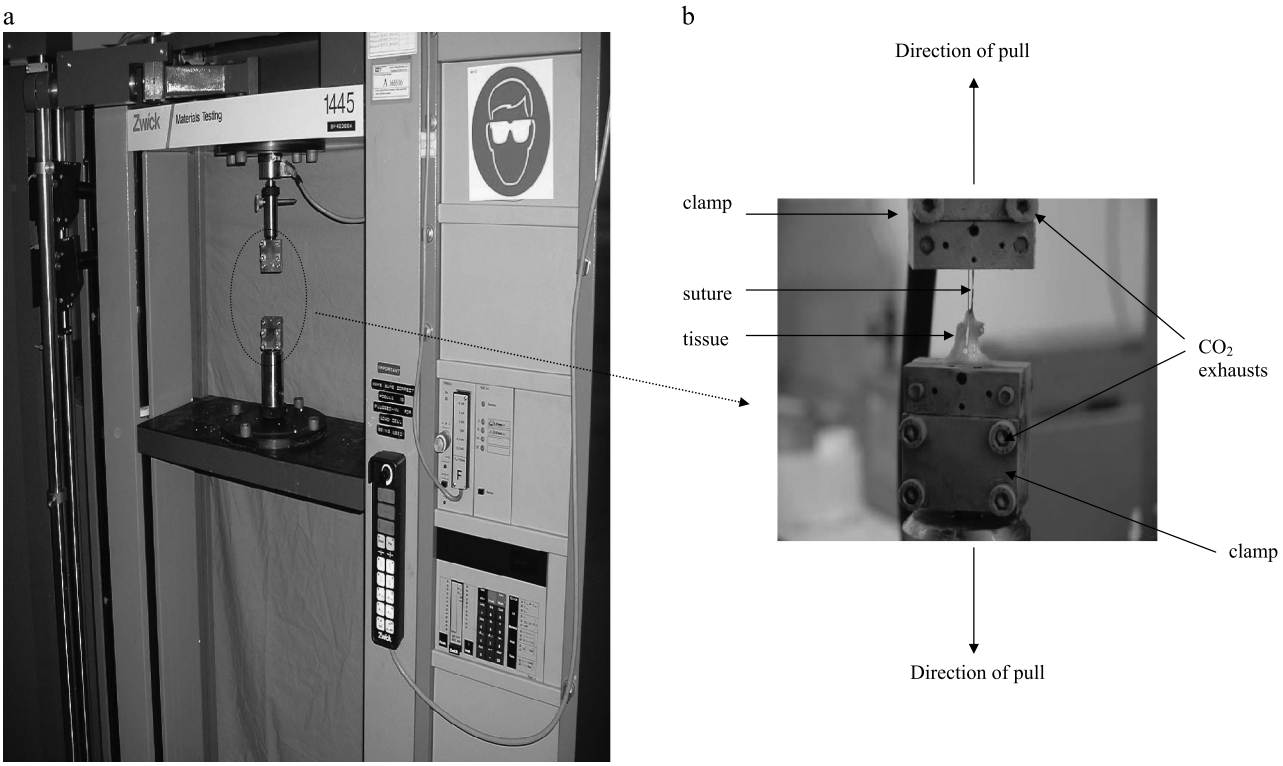


Figure 1. a. Zwick (1445) materials testing machine. b. Clamps securing tissue during suture pull-out test.

between yield and tissue stiffness (r = 0.6130), CD (r = 0.5306) and maximum load (r = 0.9510), and stiffness, maximum load (r = 0.5214) and CD (r = 0.5443). Calcific degeneration was also found to have a positive correlation with maximum load (r = 0.5583). Age, gender and valve site were not identified as significant in determining initial yield, tissue stiffness nor maximum force required for total destruction in either the univariate or correlation analyses.

Two tissue samples were excised from patients with known episodes of IE. The first tissue sample, excised from a 71-year-old male who had an episode of IE three months previously and a diagnosis of AS and myxomatous degeneration yielded at 2.0 N and ruptured totally at a maximum load of 3.6 N. The second tissue sample excised from a 54 year-old-male with a recent episode of IE but no other valve diseases yielded at 0.24 N, well below the minimum mechanical forces of the beating heart, and ruptured totally at a force of 1.4 N (Table 1). Although the analysis revealed a negative coefficient for IE, confirming a failure rate below the average, this was found not to be significant.

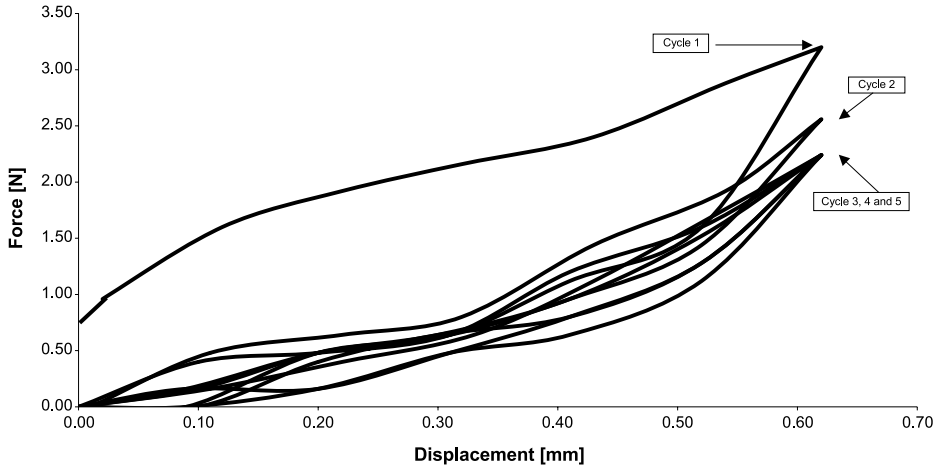
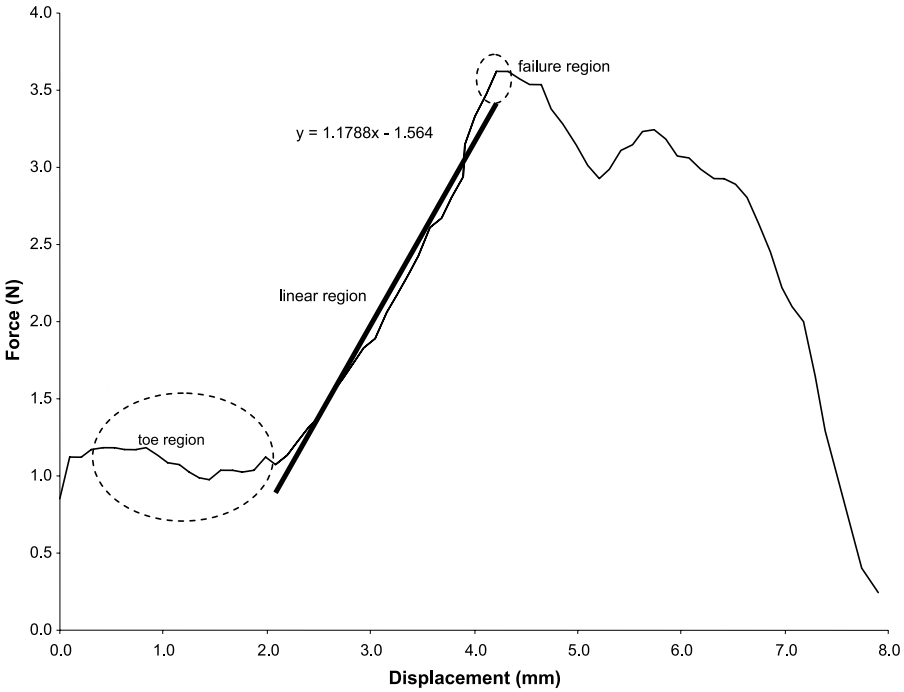


Figure 2. Preconditioning of tissue.



y = the slope denoting the stress/strain relationship for a material under uniaxial force i.e. stiffness

Figure 3. Failure pattern of human cardiac valve tissue.

4. Discussion

The results shown in Table 1 suggest the forces required to cause a single suture to yield and pull completely away from the surrounding tissue are comparable with the minimum mechanical forces associated with the beating heart (14, 15). A suture placed in tissue known to have had a recent episode of IE yielded at a significantly lower force, suggesting the risk of partial or total valve dehiscence is very high in patients with or at increased risk of developing prosthetic valve endocarditis, such as the elderly and those with multiple valve prostheses (PVE)[f] (14, 15, 23). However, cardiac prosthesis are customarily secured in place by at least 14 sutures, thereby, distributing the load and reducing the risk of dehiscence. A previous study showed magnetically induced forces acting on cardiac implants at 4.7 T are at least one-thousand times smaller than the mechanical forces of the naturally beating heart (14, 15). Therefore, forces required to cause total detachment from the surrounding tissue will be significantly smaller than magnetic field induced forces observed at 4.7 T. Due to the paucity of tissue samples available for study, it is, however, inappropriate at this stage to draw any firm conclusions about the effects of magnetic forces acting on infected tissue as these results cannot currently be supported.

Advancing age is known to decrease collagen in human cardiac valves (24–26), increase tissue stiffness and reduce distensibility and flexibility. Smaller forces are therefore required to cause tissue to permanently distend beyond the point of return thereby increasing the risk of tissue tearing. Our study identified tissue stiffness as a significant factor in determining the strength of force required to cause initial yield and total destruction. Although the study did not investigate collagen levels, it nonetheless determined, to some degree, the level of calcification which appears to directly influence tissue strength and stiffness. Heavily calcified and stenosed tissue samples demonstrated a greater stiffness and rigidity compared with non- or less heavily calcified tissue samples. Research has suggested increases in tissue stiffness are age and gender related (24–28) as well as being type specific, i.e., central versus muscular arteries (29) or mitral versus aortic valves (24). Senile calcific aortic stenosis (i.e., degenerative aortic stenosis) usually occurs in patients aged $\geq$ 60, and this type of aortic stenosis is frequently combined with calcification of the mitral valve annulus which causes narrowing of the valve orifice (23). However, we did not find any correlation between increasing age, gender and stiffness ($r = 0.27$ and $r = 0.08$ respectively) or, stiffness and valve site ($r = 0.26$).

Although we have not studied the potential effects of suturing on tissue strength, research has shown a puncture/suture hole weakens tissue by as much as 22–59% (30–32). We believe, however, that tissue surrounding the puncture/

[f]Prosthetic valve endocarditis is located in the sewing ring and always involves para-valvular tissues which undermines the attachment of the valve, often leading to necrosis with abscess formation.

Table 1. Maximum force required for to tissue yield and to total rupture

Patient/disease profile					Results				
Patient no.	Age (years)	Gender	Valve site	Valve pathology	Yield point (N)	Force/displacement (stiffness) (N/mm)	Max load single suture (N)	Calculated max load 14 sutures (N)	Mechanical forces of beating heart (N)*
1	56	Female	Mitral	Regurgitation, degeneration	3.37	1.18	3.62	50.62	2.7–21.1
2	89	Female	Aortic	Stenosis	1.60	0.56	2.14	30.02	2.6–10.3
3	71	Male	Aortic	Stenosis	2.46	4.69	2.64	36.96	2.6–10.3
4	78	Male	Aortic	Stenosis	8.78	1.50	9.49	132.83	2.6–10.3
5	65	Male	Aortic	Myxomatous degeneration, stenosis	3.18	1.14	3.66	51.30	2.6–10.3
6	69	Male	Aortic	Stenosis	3.31	1.25	3.76	52.64	2.6–10.3
7	59	Female	Aortic	Stenosis	8.43	2.26	12.96	181.44	2.6–10.3
8	71	Male	Aortic	Stenosis, myxomatous degeneration, episode endocarditis	2.00	4.17	3.60	50.40	2.6–10.3
9	72	Male	Aortic	Calcific degeneration	1.36	0.14	1.36	19.04	2.6–10.3
10	74	Male	Aortic	Stenosis	3.12	4.13	3.44	48.16	2.6–10.3
11	70	Male	Mitral	Severe calcification	3.76	3.78	4.40	61.60	2.7–21.1
12	82	Female	Aortic	Calcific degeneration, stenosis	3.04	5.12	3.44	48.16	2.6–10.3
13	44	Male	Aortic	Severe stenosis, congenital	3.12	3.83	5.68	79.52	2.6–10.3
14	76	Male	Mitral	Severe calcification	14.00	9.82	14.00	196.00	2.7–21.1
15	62	Female	Mitral	Myxomatous degeneration, calcification	5.04	3.83	5.04	70.56	2.7–21.1
16	29	Male	Mitral	Stenosis	1.68	0.73	3.12	43.68	2.7–21.1
17	65	Male	Aortic	Severe calcification	3.92	3.61	4.56	63.84	2.6–10.3
18	54	Male	Aortic	Previous infection	0.24	0.10	1.36	19.04	2.6–10.3

*Mechanical force of the beating heart is calculated by multiplying the aortic/ventricular pressure difference (at end systole) by the area of the closed valve.

suture hole will not remain an area of significant weakness in the long-term as tissue re-grows and endothelization occurs within 6–8 weeks after implantation (33). As a result of the difficulties of obtaining tissue samples from patients who had undergone surgery to replace a prosthetic heart valve (i.e., presence of scar tissue), we are unable to report on the tensile strength of scar tissue. However, research shows scar tissue can be significantly stronger than non-scar tissue (34). We can only surmise, therefore, that cardiac valvular tissue scarred by previous surgery behaves similarly and becomes less susceptible to tearing at normal or magnetically induced forces.

5. Conclusion

The conclusions of the study are limited due to the small sample size. Furthermore, the sample is heterogeneous, a factor which could not be controlled for. Despite these limitations and the study's failure to demonstrate any definitive correlation between age and stiffness, we should not be dismissive of the suggestion of a relationship. Cardiac valve pathology is such that senile calcific aortic stenosis usually occurs in elderly patients, i.e., $\geq$ 60 years, and results from a gradual build-up of calcium deposits leading to a narrowing of the valve annulus. Over time, tissue becomes more rigid and stiffer and requires increasing forces to achieve total suture/tissue destruction. Thus, patients suffering from age-related stenosis and/or calcification of the valve annulus would be unlikely to be at risk of partial or total valve dehiscence whilst undergoing MRI $\leq$ 4.7 T. Similarly, tissue scarred by previous surgery also becomes more rigid and stiffer and would therefore be unlikely to pose a risk to patients exposed to MRI $\leq$ 4.7 T. Although the endocarditic tissue sample failed at a significantly lower force than tissue with other valve pathologies, it is impossible, at this stage, to make any definitive conclusions whether this pathology is more likely to cause partial or total valve dehiscence during MRI.

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