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Original Article

Patient-specific Prediction of Intrinsic Mechanical Loadings on Sub-muscular Pectoral Pacemaker Implants based on an Inter-species Transfer Function

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Abstract

With the steady technological development enabling reduced device dimensions and new patient populations, detailed data on mechanical *in vivo* loads become increasingly important to ensure reliability of implantable medical devices. Based on an intra-species correlation of in-line and transverse force of the *Pectoralis major* established previously for the Chacma baboon (de Vaal et al., 2010a), a simplified physiological model and a mechanical equivalent model were developed for a sub-muscular pectoral device implant considering *Pectoralis major*, *Pectoralis minor* and rib cage. By assessing the morphometric and mechanical parameters of these musculo-skeletal structures and the associated model parameters, the intra-species correlation was shown to exhibit a) robustness for a larger intra-species subject population and b) linear scale variance allowing the application to humans under consideration of the inter-species difference of the attachment angles of the *Pectoralis major*. The transfer function provides a basis for the prediction of patient-specific maximum mechanical loadings on a sub-muscular pectoral cardiac pacemaker implant through non- or minimal invasive measurements on the patient.

Keywords: scaling; transfer function; mechanical loading; pacemaker;

Abbreviations

CT	Computed tomography
IPM	Instrumented pacemaker
MLR	Multiple linear regression
PCSA	Physiological cross-sectional area
Pmajor	*Pectoralis major*
Pminor	*Pectoralis minor*
VHM	Virtual Human Male (Spitzer et al., 1996)

Symbols

a_i	Coefficients of inter-species transfer function where i = 1 to 5
F_{IL}	In-line force generated in the sternal *Pectoralis major*
F_T	Transverse force acting on the IPM / pectoral implant
k_r	Transverse stiffness coefficient of the rib cage
k_{t1}	Transverse stiffness coefficient of the *Pectoralis major*
k_{t2}	Transverse stiffness coefficient of the *Pectoralis minor*
L_f	Muscle fibre length
$L_{f,opt}$	Optimal muscle fibre length
L_m	Length of the sternal *Pectoralis major* along the estimated line of action
L_r	Characteristic length of the rib cage determined by the rib geometry and curvature
M_b	Body mass of subject
M_m	Mass of the entire *Pectoralis major*
n	Number of subjects
Q_{IL}	Uniformly distributed in-line force along the width of the *Pectoralis major* over the pectoral implant
t_m	Thickness of the sternal *Pectoralis major* at the location of the IPM / pectoral implant
$t_{m,cb}$	Thickness of the sternal *Pectoralis major* at crossbar of the buckle force transducer
t_{mu}	Thickness of the *Pectoralis minor* at the location of the IPM implant
V_m	Volume of the entire *Pectoralis major*
w_m	Width of the *Pectoralis major* over the IPM / pectoral implant
$w_{m,cb}$	Width of the *Pectoralis major* at the cross bar of the buckle transducer
ψ_1	Angle of attachment of the *Pectoralis major* at its origin

$\overline{\psi}_1$ Mean angle of attachment of the *Pectoralis major* at its origin for n subjects

ψ_2 Angle of attachment of the *Pectoralis major* at its insertion

$\overline{\psi}_2$ Mean angle of attachment of the *Pectoralis major* at its insertion for n subjects

ρ_m Material density of *Pectoralis major*

σ_m Axial stress in the *Pectoralis major* during contraction

σ_{mu} Axial stress in the *Pectoralis minor* during contraction

Subscripts

B Baboon

H Human

1 Introduction

Significant clinical benefits compared to pharmacological treatment (Cleland et al., 2005) as well as the reduction of the mortality in high-risk patient populations (Maisel et al., 2006) have been reported for implantable pulse generators (i.e. pacemakers) and implantable cardioverter defibrillators. New technologies allowing for smaller devices (Furman, 2002; Shmulewitz et al., 2006) and clinical progress has lead to a higher feasibility of implantable cardiac rhythm management in younger patients (Antretter et al., 2003; Furman, 2002).

The pectoral region has been the most common implant position for cardiac pacemakers due to fewer complications compared to the abdominal implants (Kron et al., 2001). The sub-cutaneous and sub/intra-muscular positions have been used for pectoral implants. For both, the pacemaker is placed in a tissue pocket either between the skin layer and the sternal *Pectoralis major* (*Pmajor*) for sub-cutaneous placement, or between the sternal *Pmajor* and the *Pectoralis minor* (*Pminor*)/ rib cage for sub/intra-muscular placement (Kistler et al., 2004).

Smaller implant structures combined with different levels and patterns of physical activity of the recipients bring upon altered demands for structural integrity and reliability of the devices. While structural reliability of pacemaker leads has been studied extensively (Baxter and McCulloch, 2001; Fortescue et al., 2004; Hauser et al., 2007), research towards the mechanical *in vivo* conditions of the pacemaker structure is scarce. The availability of such data, and in particular maximum levels of mechanical loadings, is however important if not crucial for the mechanical design of implants with reduced size while ensuring reliability. We have, therefore, recently demonstrated for the first time the feasibility of a system to assess *in vivo* mechanical forces on implanted pacemakers and established in the non-human primate model an intra-species correlation between the force of the sternal *Pmajor* in line of its action and the transverse reaction force on a pectoral implant in sub-muscular position (de Vaal et al., 2010a; de Vaal et al., 2010b).

The current study was concerned with the development of a transfer function which entails the extension of an intra-species relationship for in-line and transverse force of the *Pectoralis major* in baboons to humans. The proposed transfer function will provide the basis for the clinical quantification of mechanical forces on pacemaker implants by measuring the in-line force of the

Pectoralis major in patients using non- or minimally invasive methods such as electro-myography.

2 Methods

2.1 Assessment of Pectoral Anatomy in Baboon and Human

After conclusion of a related study (de Vaal et al., 2010a), two Chacma baboons (M_b=23.9±1.2kg) with pectoral sub-muscular implants of instrumented pacemakers (IPM) underwent imaging of the thoracic region with computed tomography (Aquilion 4, Toshiba Medical Systems, Zoetermeer, Netherlands) within two hours of euthanisation. Subsequently, the *Pmajor* was dissected and morphometric details were recorded as described by de Vaal (2010a): length along the estimated line of action L_m, thickness and width at the crossbar of the buckle force transducer $t_{m,cb}$ and $w_{m,cb}$, and width over the IPM implant w_m. After excision, mass M_m and volume V_m of the muscle were recorded.
Using Mimics® (Materialise BV, Leuven, Belgium), the location of the IPM and surrounding musculoskeletal structures were reviewed in axial and sagittal cross-sectional views of baboon and human [Virtual Human Male (VHM), Visible Human Project, National Library of Medicine National Institutes of Health, Bethesda, MD, USA; (Garner and Pandy, 2000; Spitzer et al., 1996)] CT imaging data. In VHM images, the position of a pectoral sub-muscular pacemaker implant was estimated according to Brinker and Midei (2005). Comparative anterior-posterior and lateral measurements for baboon and human were obtained from axial views. A 3D representation of skeletal anatomy of one baboon with IPM implant was obtained by reconstruction from a CT image set using thresholding operations in Mimics®.

2.2 Simplified Model of Sub-muscular Pectoral Implant

A simplified representation of a sub-muscular pacemaker implant was proposed to facilitate the evaluation of influence of individual parameters on the mechanical loading on the implant. The representation was limited to the instance of the muscle contraction. This limitation was deemed sufficient for quasi-static loading, disregarding mass or damping effects, based on two assumptions. Firstly, the IPM was exposed to a load at rest, i.e. the muscle was compressed prior to contraction. Secondly, the effects of load rate and fibre orientation on the viscoelastic behaviour of passive muscle under compression (Van Loocke et al., 2008) can be neglected since, in our experiments, the muscle was active with increased stiffness compared to passive state and the compression acted in cross-fibre direction with lower stiffness and viscosity compared to the fibre direction. The muscle contraction was sustained for approximately 0.5s only (de Vaal et al., 2010a) and the compression rate was similar to that for contraction of a relaxed muscle to maximum level of $200s^{-1}$ (Wilkie, 1949). This value was considerably higher than the rate reported by Van Locke et al. (2008) for which they reported that the reaction of passive muscle to compression was devoid of viscous effects for instantaneous loadings.

Figure 1(a) illustrates a simplified physiological model: The IPM resting on *Pminor*, supported by rib cage, is compressed by the *Pmajor*. The mechanically equivalent model is illustrated in Figure 1(b) indicating parameters considered to affect the normal force F_T in the two-dimensional case: in-line force F_{IL} generated in the *Pmajor*, material properties of the anatomical structures surrounding the IPM, and angles of attachment of the *Pmajor* from the IPM location to origin and insertion of the muscle, ψ_1 and ψ_2, respectively. In the three-dimensional case, the interplay between width of the *Pmajor* over the implant, w_m, and the force uniformly distributed along this width, Q_{IL}, with

$$\mathrm{Q_{IL}} = \frac{\mathrm{dF_{IL}}}{\mathrm{dw_m}} \tag{1}$$

was assumed to affect F_T due to the muscle contraction causing a concentrated muscle mass around the line of action. The IPM was considered to be a rigid structure. The transverse viscoelastic properties of *Pmajor* and *Pminor* (Van Loocke et al., 2008) were simplified as transverse stiffness k_{t1} and k_{t2}, respectively. The transverse stiffness of the rib cage (Viano and King, 2000) was simplified as transverse stiffness k_r.
The experimental measurement of in-line force F_{IL} and transverse force F_T of the *Pmajor sternum* in the baboon in a related study has been described in the Supplement and in detail by de Vaal et al. (2010a).

2.3 Intra-species and Inter-species Evaluation of Model Parameters

An intra-species correlation of morphometric parameters and F_{IL} with the transverse force on the pacemaker, F_T, has been reported by de Vaal et al. (2010a):

$$\mathrm{F_T} = -1055.78 - 0.24\,\mathrm{F_{IL}} + 3.24\mathrm{L_m} + 5.95\,\mathrm{w_m} + 434.62\,\sigma_\mathrm{m}\ . \tag{2}$$

The difference of morphometric and mechanical parameters between subjects and the influence of the model parameters on F_T were evaluated intra-specifically (between baboons) and inter-specifically (between baboons and humans). The following subject populations were considered

- Baboons: adult males, $M_b \approx 24$kg (de Vaal et al., 2010a),
- Humans: adult males, $M_b \approx 90$kg (Spitzer et al., 1996).

Musculoskeletal material parameters were comparable between baboons and humans based on similarity of mammalian musculoskeletal tissue (Biewener, 2000). The evaluation of each model parameter for the intra-species and inter-species effect on F_T was conducted by assuming that all model parameters, except the one under evaluation, remained constant, and ascertaining whether the influence of the variance of this parameter within the subject population had a strong (significant) or weak (insignificant) effect on the magnitude of F_T.

For the intra-species baboon case, the strength of the effect (weak or strong) of a parameter on F_T was based on a) whether or not it was represented in Eq. (2), b) experimental findings and/or c) data from literature. For model parameters not studied in our intra-species MLR analysis (de Vaal et al., 2010a), weak intra-species influence on F_T was assigned based on the following considerations:

- t_{mu} and σ_{mu}: Due to the non-linear elastic properties of passive muscle and $F_{Trest} > 0$, a sufficiently high stiffness k_{t2} was assumed, minimizing a change of t_{mu} during contraction of *Pmajor*. Combined with the indication that $t_{m,cb}$ had no intra-species effect on F_T, see Eq. (2), and $t_{mu} < t_{m,cb}$, a weak influence of t_{mu}, and similarly of σ_{mu}, on F_T was assumed.
- k_r: Based on high values of stiffness and damping of the human chest (Viano and King, 2000), a weak influence on F_T was assumed for k_r. For baboons, this was supported by the fact that the shoulder was allowed to move freely during electrical stimulation (de Vaal et al., 2010a), causing a lower compression on the ribs compared to an isometric contraction (with shoulder and sternum fixed).
- ψ_1 and ψ_2: Since F_T and F_{IL} were evaluated only at maximum level of contraction and the shoulder complex was free to move during electrical stimulation, subject-specific differences for ψ_1 and ψ_2 in the contracted muscle state were assumed to be negligible.
- Q_{IL}: The uniform distribution of F_{IL} based on an uniform distribution of motor units within the cross section of the activated muscle region (Knaflitz et al., 1990) was assumed to have a weak influence on F_T.

Adopting the reasoning for the intra-species case, parameters with weak intra-species effect on F_T were also assumed to exhibit a weak inter-species effect on F_T. Due to the considerable difference in the torso geometry between baboon and human, a strong inter-species influence on F_T was, however, assumed for ψ_1 and ψ_2.

2.4 Assessment of Suitability of Baboon Intra-species Correlation for Humans

The intra-species correlation established for baboons was considered to be suitable for humans if the differences of morphometric and mechanical parameters between baboons and humans were proportional to differences of the corresponding model parameters. The assessment included causative parameters with a) significant intra-species effect on F_T, see Eq. (2), and b) unknown effect on F_T, namely PCSA, $t_{m,cb}$, t_{mu}, σ_{mu}, ψ_1 and ψ_2.

The type of relationship (linear or non-linear) between causative and model parameters established for the intra-species correlation in the robustness assessment (see Supplement) was considered equally applicable for the inter-species correlation due to the similarity of the musculoskeletal material properties between baboon and human (Biewener, 2000) and the self-similarity of the cursorial upper limbs (Voisin, 2006). Morphometric parameters without significant intra-species effect on F_T according to our previous MLR analysis (de Vaal et al., 2010a) were considered to have a negligible effect on F_T for the inter-species correlation. To account for the geometrical differences between the two species, the effect of the *Pmajor* attachment angles were employed utilizing a relationship derived from the mechanically equivalent simplified model,
Figure 1(b):

$$F_T = F_{IL}(cos\,\psi_1 + cos\,\psi_2). \tag{3}$$

Assuming that F_{IL} did not depend on ψ_1 and ψ_2, a relationship for inter-species differences can be derived from Eq. (3):

$$\mathrm{F_{T,H}} = \mathrm{F_{T,B}}\frac{(\cos\psi_1 + \cos\psi_2)_\mathrm{H}}{(\cos\psi_1 + \cos\psi_2)_\mathrm{B}}. \tag{4}$$

3 Results

3.1 Pectoral Anatomy in Baboon and Human

The baboon morphometric data are summarized in

Table 1. The position of a sub-muscular pectoral IPM implant in one baboon is illustrated in Figure 3. Cross sectional views of the pectoral region of baboon and human are shown in Figure 4. The anterior-posterior and lateral (humerus-to-humerus) distances are indicated in an axial section at the middle of the sternum and corresponding sagittal section at medial third of the clavicle is shown. The ratio of lateral to anterior-posterior distance was 15% larger in the baboon compared to the human.

3.2 Intra-species and Inter-species Model Parameters

For each parameter of the simplified physiological model of a pectoral implant, the size of intra-species and inter-species effect on F_T is given in

Table 2. The governing morphometric parameter(s) and availability of data for baboon and human is indicated for each model parameter. A strong inter-species influence on F_T was indicated for *Pmajor* model parameters, namely F_{IL}, k_{t1}, ψ_1, ψ_2, and w_m. Weak inter-species effect was indicated for Q_{IL} and parameters of *Pminor* and rib cage.

3.3 Suitability of Baboon Intra-species Correlation for Human Subjects

The outcomes of the suitability assessment of the baboon intra-species correlation for human subjects are summarized in Table 3. Proportionality between causative and model parameter was indicated for F_{IL}, L_m, w_m, and σ_m (cases A-E) based on the results of the robustness assessment (Supplement). PCSA and $t_{m,cb}$ were negligible based on their insignificant effect on F_T despite potential intra-specific variation in the baboon (cases F and G). The parameters t_{mu} and σ_{mu} were deemed negligible based on the assumptions that the *Pminor* had a negligible effect on F_T (cases H and I). The attachment angles ψ_1 and ψ_2 exhibited non-linear relationships to the associated model parameter F_T according to Eq. (3) (case J). While cases A-I supported the suitability, i.e. linear scale variance, of the intra-species correlation for inter-species correlation, case J imposed a limitation that required inclusion of a corrective term.

3.4 Inter-species Transfer Function

Figure 5 illustrates the concept of the inter-species transfer function to obtain maximum mechanical loads due to muscle contraction on a sub-muscular pectoral device implant. The principal elements of the transfer function are:

1. Experimental acquisition of *Pmajor* morphometric parameters (L_m, w_m and σ_m), F_{IL} and F_T in baboons;
2. Attainment of intra-species correlation between morphometric parameters, F_{IL} and F_T from baboon data using linear regression analysis;
3. Acquisition of *Pmajor* morphometric parameters and F_{IL} for a human subject;
4. Calculation of uncorrected F_T for human subject using intra-species correlation (step 2) with human data;
5. Correction for nonlinear relationship of ψ_1 and ψ_2 with F_T using Eq. (4).

The inter-species transfer function can be derived from Eqs. (2) and (4) as:

$$F_{T,H} = \frac{(\cos\psi_1 + \cos\psi_2)_H}{(\cos\bar{\psi}_1 + \cos\bar{\psi}_2)_B} \cdot (a_1 + a_2 F_{IL} + a_3 L_m + a_4 w_m + a_5 \sigma_m)\,, \tag{5}$$

where $\bar{\psi}_1$ and $\bar{\psi}_2$ are the average attachment angles of the *Pmajor* for baboons with $\bar{\psi}_1 = \sum_1^n \psi_1/n$ and $\bar{\psi}_2 = \sum_1^n \psi_2/n$ for n subjects. The initial coefficients values were a_1=-1055.78, a_2=-0.24, a_3=3.24, a_4=5.95 and a_5=434.62 according to Eq. (2). (Note: Eq. (5) requires the parameters to be specified in the following unit: F_{IL} in N, L_m and w_m in mm, and σ_m in N/mm^2.)

4 Discussion

In this study, an inter-species transfer function was formulated to relate the maximum active transverse force on a pectoral sub-muscular pacemaker-type implant in baboons to the equivalent force in humans. The principal elements of the transfer function concept were: 1) Intra-species correlations that identified parameters with significant effect on the transverse force F_T on the implant for each species, and 2) the inter-species relationship of these parameters, supported by anatomical and morphological similarities between baboons and humans. The soundness of the transfer function concept was confirmed using a simplified physiological model.

Due to the presence of a clavicle, the Chacma baboon was the most suitable animal model for the inter-species assessment of the *in vivo* mechanical loading on a pectoral pacemaker implant in humans. This essential resemblance to humans enabled similar movements of the upper limb not found in other laboratory animals (Voisin, 2006). The pectoral implantation site in the baboons compared very well to those of humans, relative to surrounding anatomical structures. The material density of the *Pmajor* in baboons of 1.115±0.055g/cm^3 matched values of 1.112±0.006g/cm^3 for human skeletal muscle (Ward and Lieber, 2005) and 1.0597g/cm^3 for rabbit and canine muscle accepted more generally for mammalian muscle (Mendez and Keys, 1960).

There were, however, dissimilarities between baboon and human in certain features which required compensation. The body mass for baboons was 23.9±1.2kg in this study and can vary between 15 and 31kg (Fleagle, 1999). The body mass of a human lean adult male is 60.4kg (Westerterp-Plantenga et al., 2003) while it was 90.3kg for the VHM (Spitzer et al., 1996). A degree of positive allometry was found for the upper limb of the baboon and the VHM.

Considering the *Pmajor*, the ratio of muscle to body mass was 0.0062±0.0016 for baboons and 0.0079 for the VHM with V_m=676.4cm^3 (Garner and Pandy, 2000) and density of 1.0597g/cm^3 (Mendez and Keys, 1960). Another difference was expected in the *Pmajor* attachment angles: Although not directly measured, these angles were assumed to be larger for the baboon than for the human due to different chest curvature at the implantation site.

The suitability evaluation considered morphometric/physiological parameters with significant and non-significant intra-species effect on F_T in baboons (de Vaal et al., 2010a). This was motivated by the fact that a non-significant effect of a parameter in an MLR may stem from; a) non-linear effect on F_T, b) intra-specific invariance or c) negligible or no effect on F_T. The extended assessment addressed this limitation. It was found that experimental parameters with significant effect on F_T remained proportional to their corresponding model parameters when scaled between baboon and human. Of the non-significant parameters, only ψ_1 and ψ_2 did not exhibit a linear relationship with F_T. While ψ_1 and ψ_2 have an influence on F_T according to Eq. (3), they were considered sufficiently invariant in the baboon cohort and hence without significant intra-species effect in the MLR analysis (de Vaal et al., 2010a). Due to the substantial differences between baboons and humans, it was, however, required to account for the inter-species effect of the attachment angles on F_T. However, the correction term for the attachment angles in Eq. (5) approaches unity for inter-species similarity of attachment angles which ensures validity of the proposed transfer function should future studies indicate such a finding.

The intra-species correlation was considered linearly scale variant between baboons and humans with a body mass of $23<M_b<90$kg on the condition that the effect of the *Pmajor* attachment angles was accommodated appropriately. This was achieved by extending the intra-species correlation (de Vaal et al., 2010a) with a correction term based on the mean angles of *Pmajor* attachment for the baboon cohort and subject-specific *Pmajor* attachment angles for the human. It was possible to provide a function for the prediction of F_T on a sub-muscular pectoral pacemaker implant in a patient. This function employs subject-specific morphometric and physiological parameters that can be determined non- or minimal invasively for example by electromyography or volumetric medical imaging. In addition, the function facilitates findings that the maximum muscle stress in a particular muscle is the same in different human subjects (Li et al., 2007) and does not differ significantly between males and females despite significant differences in height, weight and muscle strength (Maughan et al., 1983).

As an example of the use of this correlation, consider an in-line force of F_{IL}=462N reported for the human *Pmajor* at maximum voluntary contraction (Chang et al., 2000). With a PCSA of 18.3 cm^2 (Table 1), this force results in a stress of σ_m = 0.256 N/mm^2, based on the relationship $\sigma_m = F_{IL}/PCSA$ (de Vaal et al., 2010a). With the assumption of equal *Pmajor* attachment angles in baboon and human, i.e. $(\cos\psi_1 + \cos\psi_2)_B/(\cos\psi_1 + \cos\psi_2)_H = 1$, length of the *Pmajor* along the line of action L_m = 210 mm for an adult human (unpublished data), the width w_m = 89.4 mm (mean value for baboons from Table 1) assuming equal size of implanted pacemaker in baboon and human, the inter-species transfer function (Eq. 5) provides a transverse force F_T = 160.5 N for an adult human.

A constraint of the current study was the small experimental sample size. Further research with larger sample sizes will provide data to verify intra-species correlation and inter-species transfer function established in this study. There may also be potential to refine these relationships by quantifying and extending morphometric parameters, such as thickness of *Pmajor* and *Pminor* at the implant site, *Pmajor* attachment angles, optimal fibre length, pennation angle and parameters relating to the compliance of skeletal structures surrounding the implant. While the strength of the intra-species correlation was not affected by the estimation of the muscle parameters $L_f/L_{f,opt}$ and θ (de Vaal et al., 2010a), the quantification of these parameters can contribute to the validation of the initial values of coefficients a_i of the transfer function. The consideration of repeated load cases at sub-maximum level and potential fatigue, both of which exceeded the scope of the current study, may constitute a further beneficial extension of the presented transfer function.

5 Conclusions

The inter-species transfer function serves as basis for the prediction of patient-specific mechanical loadings, in particular maximum levels, on a sub-muscular pectoral device implants, such as cardiac pacemakers. Such data will be beneficial for the development of smaller implantable devices while ensuring mechanical integrity and reliability of current designs. The function may be refined to provide additional information such as the distribution of the force over the implant to assess bending loads while it focused at the overall transverse force on the implant at present.

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Conflict of Interest Statement

MHdV, JS, PZ and TF do not have conflicts of interest with regard to this manuscript and the data presented therein. JN and ML are inventors on related U.S. patent applications as follows: "Implantable Medical Device Including Mechanical Stress Sensors", P0023322.02, assigned U.S. Serial Number 12/767,456 (filed April 26, 2010) and "Implantable Parameter Selection Based on Compressive Force", P0023322.03, assigned U.S. Serial Number 12/767,473 (filed April 26, 2010).

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Tables

Table 1. Body mass and morphometric parameters of the *Pectoralis major* muscles of baboons and human.

Parameter	Baboon Implant No				Baboon	Human
	447C	447A	449C	449A	Overall[#]	
M_b [kg]	24.7		23.0		23.9 ± 1.2	~90[(1)]
M_m [g]	82	154	125	166	131.8 ± 37.4	716.8[(2)]
V_m [cm^3]	70	135	120	150	118.8 ± 34.7	676.4[(3)]
ρ_m [g/cm^3]	1.171	1.141	1.042	1.107	1.115 ± 0.055	1.060[(4)]
$t_{m,cb}$ [mm]	5	4	4	6.5	4.9 ± 1.2	- [(5)]
$w_{m,cb}$ [mm]	42.5	60	47.5	50	50.0 ± 7.4	- [(5)]
w_m [mm]	92.5	95	90	80	89.4 ± 6.6	- [(5)]
L_m [mm]	150	150	170	180	163 ± 15	- [(5)]
PCSA* [cm^2]	7.7	14.8	11.6	13.7	12.0 ± 3.1	18.3[(6)]

*with the assumption of $L_f/L_{f,opt} = 1$

[#] mean ± standard deviation

[(1)] (SpitzerSpitzer et al., 1996)

[(2)] $M_m = \rho_m V_m$

[(3)] (Garner and PandyGarner and Pandy, 2000)

[(4)] (Ward and LieberWard and Lieber, 2005)

[(5)] to be measured

[(6)] (Chang et al., 2000)

Table 2. The intra-species and inter-species difference of parameters of the simplified physiological model and the strength of their effect on the transverse force F_T. For each model parameter, the governing morphometric and mechanical parameter(s) and the availability of data for baboon and human is indicated.

MODEL PARAMETER	**MORPHOMETRIC AND MECHANICAL PARAMETERS**				
	Governing Parameter	**Availability of data**		**Effect on F_T**	
		Baboon	**Human†**	**Intra-species**	**Inter-species**
F_{IL}	F_{IL}	x		Strong	Strong
	PCSA	x	x	Strong	Strong
k_{t1}	$t_{m,cb}$	x		Weak	Weak
	σ_m	x		Strong	Strong
k_{t2}	t_{mu}			Weak	Weak
	σ_{mu}			Weak	Weak
k_r	L_r			Weak	Weak
ψ_1, ψ_2	ψ_1, ψ_2			Weak	Strong
w_m	w_m	x		Strong	Strong
Q_{IL}	F_{IL}, t_m, w_m			Weak	Weak

†VHM.(Garner and Pandy, 2000) Obtaining additional morphometric measurements from the raw VHM data set was beyond the scope of this study.

Table 3: Causative parameters and associated model parameters included in assessment of the suitability of the baboon intra-species correlation (Eq. 2) for humans and the type of their inter-species relationship. It is also indicated whether a combination of causative and model parameter was included in the intra-species regression analysis.(de Vaal et al., 2010a) A linear inter-species relationship supported suitability of the baboon intra-species correlation for humans.

Case	**Causative parameter**	**Model parameter(s)**	**Included in intra-species MLR analysis***	**Inter-species Relationship**
A	F_{IL}	F_{IL}	Yes	Linear
B	L_m	F_{IL}	Yes	Linear
C	w_m	w_m	Yes	Linear
D	σ_m	F_{IL}	Yes	Linear
E	σ_m	k_{t1}	Yes	Negligible
F	PCSA	F_{IL}	Yes	Linear
G	$t_{m,cb}$	k_{t1}	Yes	Negligible
H	t_{mu}	k_{t2}	No	Negligible
I	σ_{mu}	k_{t2}	No	Negligible
J	ψ_1, ψ_2	ψ_1, ψ_2, F_T	No	Nonlinear

* Described in de Vaal et al.(2010a)

Figures

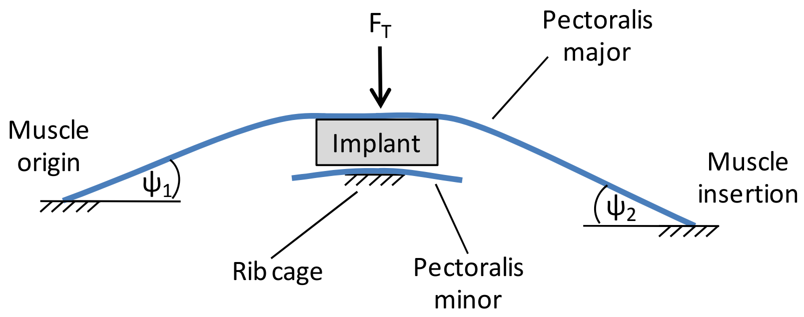

Figure 1. Simplified physiological representation of a sub-muscular pectoral pacemaker implant situated between the *Pectoralis major* and the *Pectoralis minor* resting on the rib cage.

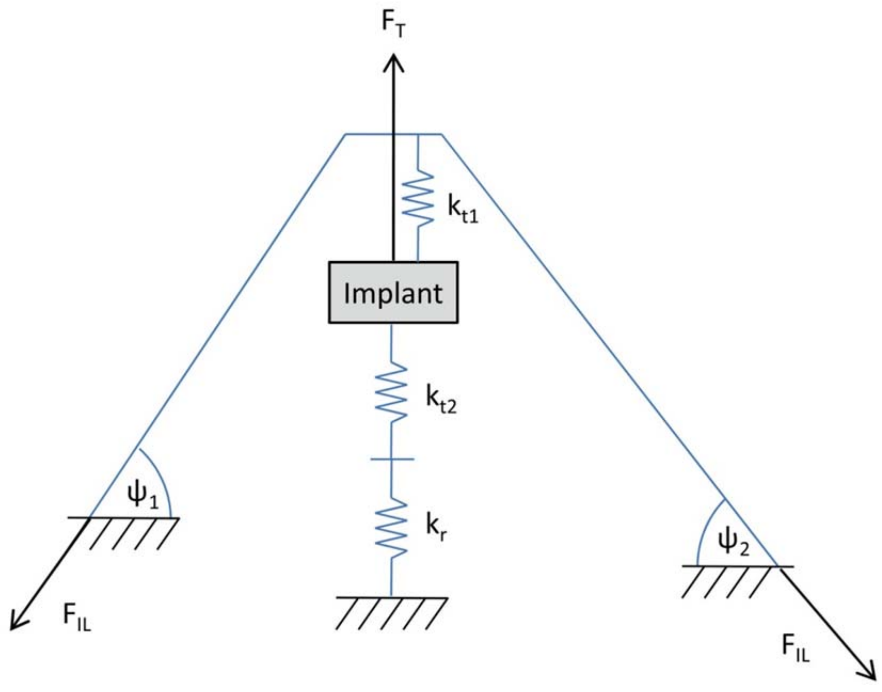

Figure 2. Mechanical equivalent of the simplified physiological model of a sub-muscular pectoral implant indicating the transverse force F_T on the implant and parameters that affect the magnitude of F_T.

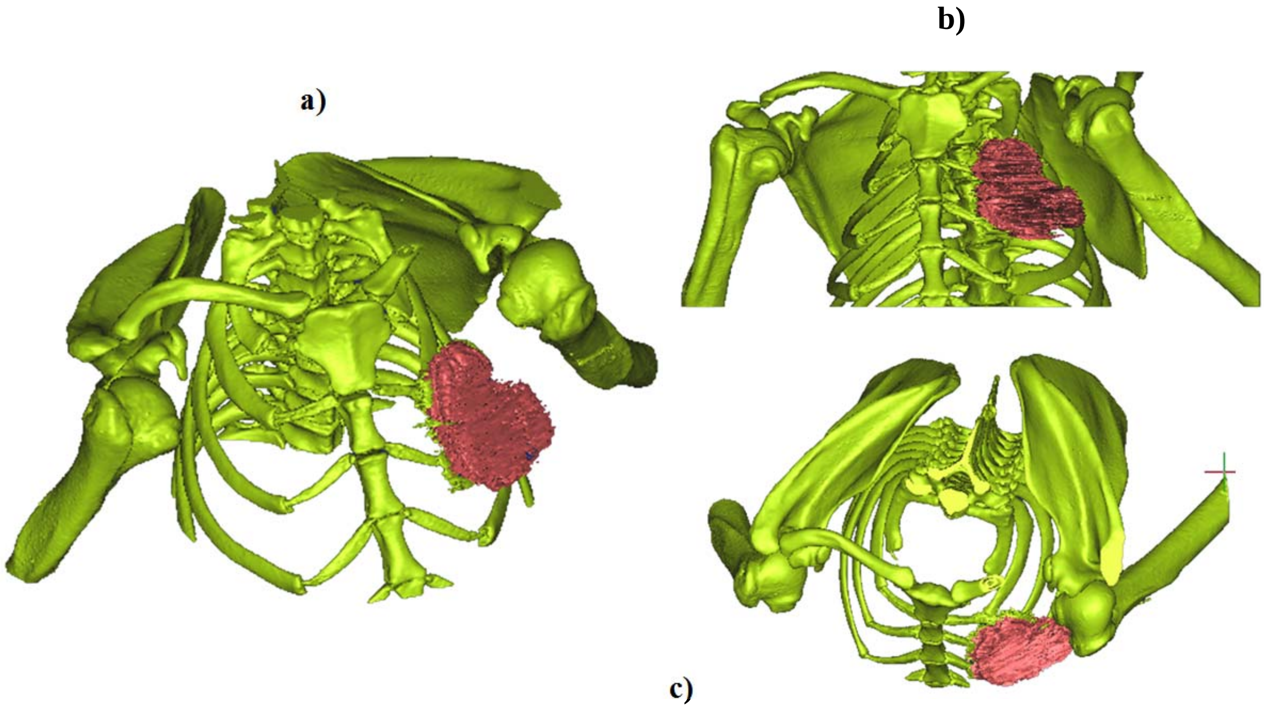

Figure 3. 3D reconstruction of thoracic skeletal structures and pectoral IPM implant (arrow) of a baboon from CT data: a) isometric view, b) frontal view and c) top view. (Imaging artifacts in the CT data were responsible for the poor resolution of the implant compared to the skeletal structures).

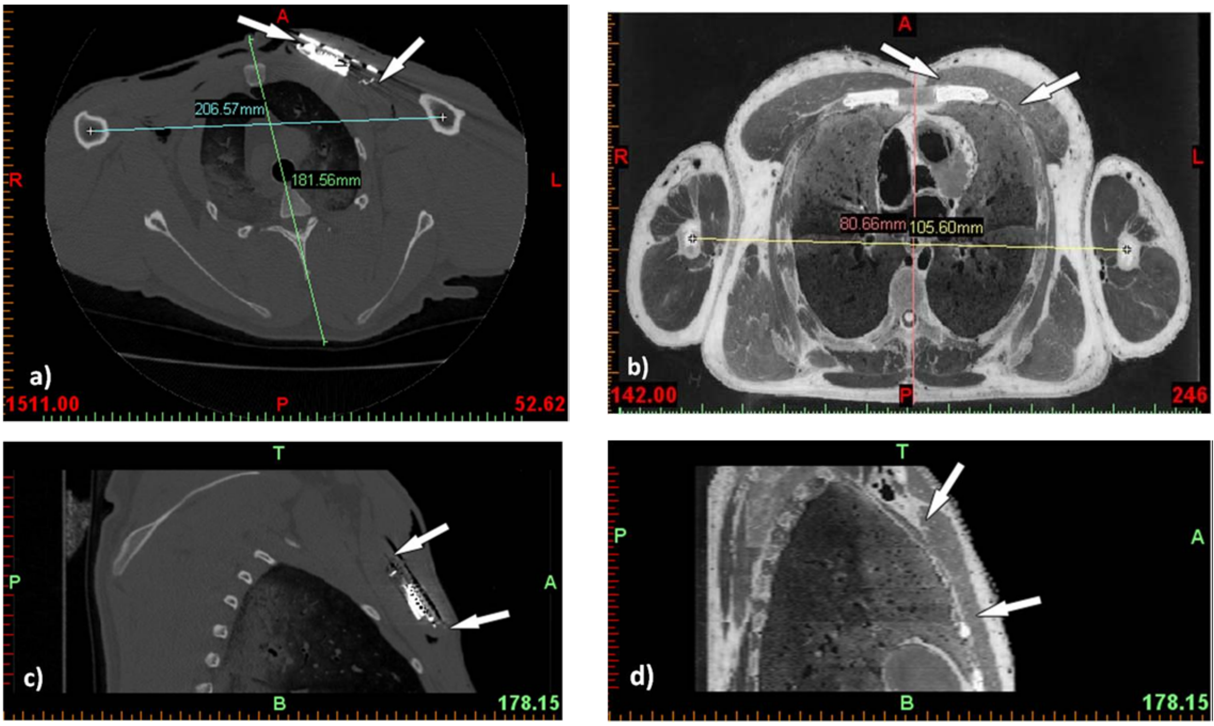

Figure 4. Cross sectional views of the pectoral region of the baboon and human.(Spitzer et al., 1996) The anterior-posterior (front-to-back) and lateral (femur-to-femur) distances are indicated in axial section at the middle of the sternum for baboon (a) and human (b). The corresponding sagittal section at medial third of the clavicle is shown for baboon (c) and human (d). Note that axial distances were not according to same scale for baboon and human and baboons; however only the ratio of measurements were used. The position of the IPM implant in the baboon is indicated with the white arrows (a, c). For human (b, d) the estimated position (Brinker and Midei, 2005) is indicated.

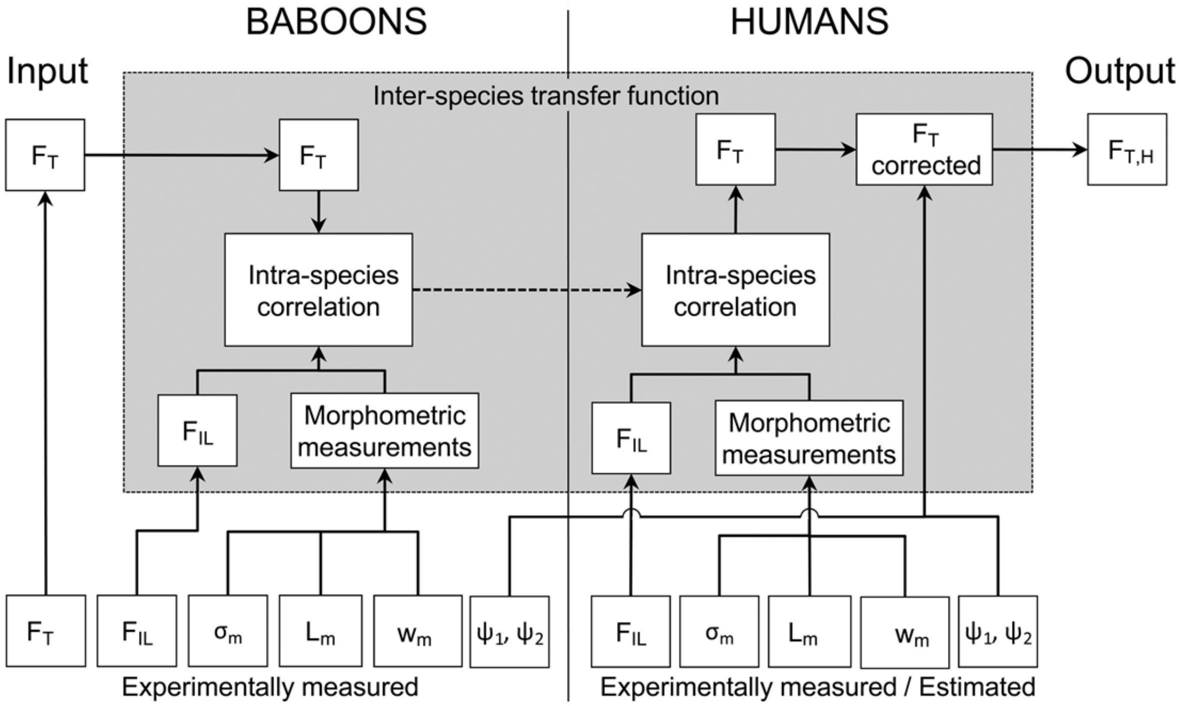

Figure 5. Diagram illustrating the inter-species transfer function for the correlation of the transverse force F_T on a sub-muscular pectoral pacemaker implant in baboons and humans.

Patient-specific Prediction of Intrinsic Mechanical Loadings on Sub-muscular Pectoral Pacemaker Implants based on an Inter-species Transfer Function

SUPPLEMENT

1 *In vivo* Measurement of In-line and Transverse for of the *Pectoralis Major Sternum*

1.1 System for Measurement of In-line Muscle Force

A custom-made stainless steel buckle transducer with closed rectangular frame (66 x 100 mm, 4 x 4 mm cross-section), removable cross bar (semi-circular cross section: R = 2 mm) and two linear foil strain gauges (EA-DY-125BT-350, Vishay Micro Measurements Group, Malvern, PA) was utilized for the measurement of the in-line force associated with muscle contraction. The strain gauges were operated with a custom-built Wheatstone half-bridge amplifier connected to a PC Laptop (Dell Latitude M65, Dell, Round Rock, TX). Data acquisition was performed using a custom code in LABVIEW (National Instruments Corp, Austin, TX). The buckle transducer was calibrated with a wire fed through frame and crossbar while tension force on the wire was induced and monitored in a standard tensile tester.

1.2 System for Measurement of Transverse Muscle Force

The wireless *in vivo* measurement system comprised an implantable instrumented pacemaker (IPM) and a radio-frequency (RF) control and data acquisition system. The IPM was a medical grade epoxy cast (dimensions: 64 x 61 x 11 mm, volume: 29 cm^3), resembling a typical commercial pacemaker housing, containing six custom manufactured contact force sensors (Tekscan, Boston, MA) with Titanium cover plates, a three-axis accelerometer (Freescale Semiconductor, Tempe, AZ), RF transceiver, micro-controller, real-time clock and high energy lithium battery. The RF data transmission system comprised a custom built RF transceiver and a

PC laptop (Dell Latitude, Dell, Round Rock, TX) linked through a serial RS232 connection. A custom software code (LABVIEW, National Instruments Corp, Austin, TX) was used to control the IPM circuitry and the data acquisition.

Raw voltage data of the force sensors was median filtered to reduce noise levels and converted to force data employing a custom algorithm (de Vaal, 2009) in MATLAB (MathWorks Inc, Natick, MA). Assuming an equal distribution of the compressive force acting in the normal direction on the in-plane surface of the IPM, the total transverse force F_T was calculated from the individual forces recorded with the six sensors, F_{Si}, the surface areas of the sensor cover plates, A_{Si} and the total area of the IPM in-plane surface A_{IPM} to the sum of the areas of the sensor cover plates:

$$F_T = \frac{A_{IPM}}{\sum_{i=1}^{6} A_{Si}} \sum_{i=1}^{6} F_{Si} \, . \tag{S1}$$

A detailed description of the system as well as the preconditioning and calibration procedures can be found in de Vaal (2009) and de Vaal et al. (2010a).

1.3 Electrical Stimulation and Measurement of Forces

The *in vivo* experiments were approved by the institutional review boards of the University of Cape Town. Under full anaesthesia, two senescent *Chacma* baboons (implant mass: 23.9 ± 1.2 kg) received one instrumented IPM unilaterally in the upper pectoral region. The IPM was implanted in the sub-muscularly position with the force-sensing surface facing outwards and secured in place with two sutures. The procedures were performed using standard surgical techniques for the implantation of cardiac pacemakers. Ten weeks after implantation, with the IPM implants having obtained fibrous encapsulation, the *Pectoralis major* muscle was exposed by removing overlying skin with the animals under full anaesthesia. The muscle was isolated from surrounding soft tissue. Two incisions were made in the fibre direction of the muscle extending from the IPM implant towards the insertion of the muscle to attach the buckle force transducer. The frame of the buckle transducer was positioned over the muscle section between the incisions and secured in place with the crossbar. Pre-gelled disposable adhesive surface electrodes (Model 9013S0211, Medtronic Inc, Minneapolis, MN) were attached to the exposed *Pectoralis major* muscle near its origin and insertion for electrical stimulation.

Constant frequency train (CFT) stimulation of the *Pectoralis major* was performed using a PULSAR 6bp bipolar stimulator (FHC Inc, Bowdoinham, ME) and pre-gelled surface electrodes. The muscle received trains of electrical current of constant, discrete amplitude of 3, 5, 7, 9, 11, 15, 17, 21, 23, 27, 31, 33, and 35 mA in one of two pre-determined randomized order. Each train comprised 2000 pulses with a pulse duration of 53 μs and a pulse interval of 203 μs. The selected amplitude range of the current and the randomization aimed at reaching maximum activation and minimizing fatigue, respectively, of the muscle. The arm of the baboon was constrained in the anatomical position whereas the shoulder complex was left to move freely, which led to the generation of a concentric (non-isometric) contraction of the muscle. The contractile force F_{IL} developed in the stimulated muscle was measured with the buckle force transducer. The transverse force F_T of the contracting muscle was recorded with the implanted IPM and the wire-less measurement system.

2 Assessment of the Robustness of the Baboon Intra-species Correlation

Due to the small sample size used to establish the intra-species correlation in the baboon, Eq. (2), it was desirable to assess the robustness of these findings for larger sample sizes in terms of subjects' body mass M_b. Since the established intra-species correlation is a linear relationship between causative parameters (morphometric and mechanical parameters) and response (F_T), correlation was considered robust if proportionality, i.e. a linear relationship, existed between causative parameters and the corresponding parameters of the simplified physiological model. Only causative parameters shown to have a significant effect on F_T, i.e. those captured in Eq. (2), were included in the robustness assessment. The relationship between causative parameters and corresponding model parameters was evaluated presuming that all other model parameters remained constant. The assessment incorporated the simplified physiological cross-sectional area (PCSA) defined by Holzbaur et al. (2007) as

$$\mathrm{PCSA} = \frac{\mathrm{V_m}}{\mathrm{L_m}} \cdot \frac{\mathrm{L_f}}{\mathrm{L_{f,opt}}} \tag{S2}$$

and the relationship for the axial stress in the *Pectoralis major*

$$\sigma_\mathrm{m} = \frac{\mathrm{F_{IL}}}{\mathrm{PCSA}}. \tag{S3}$$

In contrast to more comprehensive definitions of the PCSA (Powell et al., 1984), Eq. (S2) did not account for the pennation angle of the muscle fibres. This was based on the assumption that the pennation angle of the *Pectoralis major* did not differ between subjects (de Vaal et al., 2010b). The assessment also considered that the mechanical properties (i.e. density, constant stress and strain) of vertebrate skeletal muscles are generally scale-invariant while parameters involved in force generating scale proportionally to scale-variant changes in muscle fibre cross-sectional area and are therefore related to the PCSA (Biewener, 2000; Lieber and Fridén, 2000; Marden and Allen, 2002). From the latter it follows that the maximum muscle force scales linearly with the muscle's PCSA.

The outcomes of the robustness assessment of the intra-species correlation and the basis for establishing the relationship between causative and model parameters are summarized in Table S1. The proportionality of morphometric parameters F_{IL} and w_m with each acting as its own model parameter was trivial (cases A and C). The linear relationship of the length of the *Pectoralis major* along the line of action L_m and axial stress σ_m, respectively, with the in-line force F_{IL} as model parameter (cases B and D) was based on the proportionality a) between L_m and PCSA according to Eq. (S1) and b) between PCSA and the maximum isometric force of a muscle. Proportionality between the tensile stress σ_m and model parameters k_{t1} (case E) could not be ascertained. This case was subsequently neglected since the effect of the transverse stiffness k_{t1} of the *Pectoralis major* on the transverse force F_T. was small compared to the effect of the stress σ_m on F_T.

Table S1. Causative parameters and corresponding parameters of the simplified physiological model included in the robustness assessment of the intra-species correlation in baboons. A linear relationship between the causative factor and model parameter supported robustness of the intra-species correlation.

Case	Causative parameter	Model parameter(s)	Relationship
A	F_{IL}	F_{IL}	Linear
B	L_m	F_{IL}	Linear
C	w_m	w_m	Linear
D	σ_m	F_{IL}	Linear
E	σ_m	k_{t1}	Negligible

With proportionality for four out of the five significant pairs of morphometric and model parameter and one pair deemed negligible, the intra-species correlation in the baboon was considered sufficiently robust and valid for larger sample sizes, in terms of a wider range of body mass M_b, under similar conditions. Physiological parameters not included in Eq. (2) had a negligible effect on F_T and thus did not affect the robustness of the intra-species correlation.

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