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ROBUST MODEL-BASED QUANTIFICATION OF GLOBAL VENTRICULAR TORSION FROM SPATIALLY SPARSE 3-DIMENSIONAL TIMESERIES DATA BY ORTHOGONAL DISTANCE REGRESSION: EVALUATION IN A CANINE ANIMAL MODEL UNDER DIFFERENT PACING REGIMES

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Abstract

Quantification of global ventricular rotational deformation, expressed as twist or torsion, and its dynamic changes is important in understanding the pathophysiology of heart disease and its therapy. Various techniques, such as sonomicrometry, allow tracking of specific sites within the myocardium. Quantification of twist from such data requires a longitudinal reference axis of rotation. Current methods require specific positioning and numbers of myocardial markers and assumptions about temporal positional evolution that may be violated during dyssynchronous contraction. We present a new method to assess myocardial twist that makes minimal fully explicit assumptions while removing extraneous assumptions, by performing a least squares orthogonal distance regression of all position data on an ellipsoidal ventricular model. Rotational deformation is quantified in terms of the ellipsoid's internal coordinate system, allowing intuitive visualization. We tested this method on a set of sparse, noisy sonomicrometric crystal data in dogs under different pacing regimes to model dyssynchrony and cardiac resynchronization. We found that this method yielded robust and plausible data. This technique is also fully automated while identifying when data may be insufficient for reliable quantification of rotational deformation. This approach may allow future analysis of myocardial contraction with less tracking sites and relaxed positioning requirements while identifying situations where data are insufficient for reliable quantification of rotational deformation.

Keywords

ventricular torsion; ventricular twist; sonomicrometry; ellipsoid; orthogonal distance regression

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Introduction

The rotational component of ventricular wall movement during contraction and relaxation is a consequence of the geometry of ventricular muscle fiber arrangement and is known to play an important role for myocardial function in during both ejection and filling (4; 40; 42). Quantitatively, it can be described as the relative rotational angle of myocardial tissue in different orthogonal planes to the left ventricular (LV) longitudinal axis, referred to as twist, or in terms of the average rate of change of relative rotation along the LV longitudinal axis, referred to as torsion. Each of these measures can be computed from the other if the length of the longitudinal axis is known, but torsion has the advantage of being normalized to the size of the ventricle and may be more comparable between ventricles of different sizes, and even across species (19). Although LV torsion/twist has a role in understanding the pathophysiology of cardiac disease in many settings, it remains difficult to accurately quantify, with values from clinical and experimental studies varying widely (2; 6; 8; 11; 13; 14; 16; 19; 23; 28; 29; 32-36; 40; 44; 46-49; 51; 52; 56). Recently, the role of torsion in determining the efficacy of ventricular pacing regimes in improving myocardial performance during cardiac resynchronization therapy (CRT) has been studied (5; 25; 45; 59).

Available quantification methods to assess LV twist use position time-series generated by tracking specific loci in the ventricular myocardium, for example by inserting radio-opaque markers or sonomicrometric crystals, which allow reconstruction of relative 3-dimensional (3D) positions of these markers over time. More recently, imaging-based methods such as tagged magnetic resonance imaging (TMRI), and echocardiographic speckle tracking techniques have gained in prominence in these analyses (18; 22; 24; 50; 54). TMRI, in combination with advanced post-processing techniques such as displacement field estimation, simultaneously and accurately tracks many tissue sites and can be used to analyze regional deformations (38; 47). 2D ultrasound, on the other hand, is naturally limited to a single plane which corresponds to different parts of the myocardium as the heart moves due to longitudinal axis shortening, which may introduce errors in derived parameters (43). Thus, marker-based methods continue to have an important role in assessing myocardial torsion. The output of all these methods, with the exception of TMRI radially tagged specifically for torsion quantification (6; 11; 12) is a time- series of relative (sonomicrometry, echocardiography) or absolute (radio-opaque markers, MRI) 3D positions of ventricular wall sites from which LV twist or torsion has to be computed. Marker-based methods track fewer sites simultaneously than imaging based methods (typically up to approximately 15) since the markers/crystals have to physically be implanted into the myocardium, and, in the case of sonomicrometry, be connected to the measurement device.

When attempting computation of LV twist or torsion, it is crucial to recognize that rotational parameters can only be meaningfully defined with reference to a common reference axis of rotation, the choice and stability of which will critically affect the output generated. Previously described methods to compute LV twist from crystal or implantable marker data have typically required accurate and specific selection of the measurement sites. Bell et al. placed 13 ultrasonic crystals, 12 of which were arranged in 3 parallel planes, allowing them to compute torsion angles under the assumption that the planes defined by crystal positions are and remain parallel throughout the cardiac cycle (2; 3). Importantly, their method makes implicit assumptions about stability of the reconstructed 3D coordinate system, since the reference axis for torsion computation is assumed to be orthogonal to the respective plane. This assumption is poorly sustained under normal contraction and probably invalid with dyssynchronous contraction. If markers are misaligned relative to the long axis, then either longitudinal or horizontal contraction will affect torsion angle estimates. Helle-Valle et al. reported a similar arrangement of sonomicrometer crystals in parallel planes, augmented by

a coordinate interpolation scheme (18). Presumably, they used this interpolation to enforce plane parallel orientation, although this is not described in sufficient detail to be able to assess whether it addresses the problem of establishing a global rotational reference axis more robustly.

The Stanford group, working with radio-opaque markers, used an apical marker and the computed midpoint between two basal markers to define the longitudinal direction and then perform a transformation to cylindrical coordinates, allowing quantification of relative angular positions as a function of longitudinal position and LV twist (8; 14; 15). Beyar et al. used one apical radio-opaque marker together with the centroid of 4 basally positioned markers to determine the direction of the ventricular longitudinal axis (4; 14; 20). While these approaches are likely more robust to alterations of relative crystal alignment during contraction than those relying on the assumption of parallel marker planes, robust estimation of axis direction depends exclusively on the positioning of a small subset of the measurement sites and assumptions about their anatomical location.

To eliminate these potential sources of systematic error in twist quantification, and simultaneously reduce the experimental requirements with regard to measurement site positioning, we developed a novel data analysis methodology that makes the assumptions usually implicit in any LV twist calculation fully explicit. This approach should allow for robust LV twist calculation from fewer measurement sites and with relaxed requirements for specific marker location, while allowing straightforward extensions to compute robust approximations of a variety of other ventricular performance parameters.

Materials and Methods

Acquisition of test dataset

3D position timeseries for 10 sonomicrometer crystals implanted into the LV wall of an acute anesthetized open-chested canine pentobarbital-anesthetized model were recorded during RA, apical LV and free wall LV pacing with or without simultaneous high right ventricular (RV) outflow tract pacing to simulate left bundle branch block contraction patterns, such that RV-LV apical and RV-LV free wall pacing modes reflected a clinical relevant mode of cardiac resynchronization therapy (CRT) in 5 animals. Details of the experimental protocol are provided in the following two subsections. The reader is also referred to our previous publication (21).

Preparation

The protocol was approved by the Institutional Animal Care and Use Committee and conformed to the position of the American Physiological Society on research animal use. Five mongrel dogs, weighing 21.0 ± 1.5 kg were studied after an overnight fast. All dogs were anesthetized with sodium pentobarbital (30 mg·kg⁻¹ induction; 1.0 mg·kg⁻¹·h⁻¹ with intermittent boluses, as needed), their tracheas intubated (8 Fr. Portex endotracheal tube) and mechanically ventilated (Harvard dual-phase animal ventilator) with a 10 mg·kg⁻¹ tidal volume. Frequency was adjusted to maintain an arterial pCO₂ between 35-40 mm Hg. Fluid resuscitation was maintained with 0.9N NaCl at 10 ml·kg⁻¹·h. The pericardium was opened and epicardial pacemaker leads were placed on the right atrium, right ventricular free-wall near the anterior infundibulum, LV mid- free-wall near the mid-posterior-lateral wall, and LV apex for multi-site stimulation. Ten sonomicrometric crystals (Sonomicrometry, Sonometrics Corp., London, Ontario, Canada) were implanted in the mid-myocardium of dogs at the end of open chest experiments designed to evaluate the effects of various artificial pacing modes on ventricular performance through invasive and non-invasive measures of cardiac performance. Three sets of sonomicrometer crystals were placed around

the short axis of the LV mid-myocardium at three regions along the LV longitudinal axis: three apical, four mid-ventricular and three basilar sets of crystals. After crystal placement, 5 cm H₂O PEEP was applied to maintain end-expiratory lung volume for the remainder of the experiment.

Protocol

The protocol consisted of pacing and then creating a stable apneic steady state for data acquisition. To avoid retrograde conduction for all pacing steps of the protocol, RA pacing was performed at frequencies 5-10 min⁻¹ above the intrinsic rhythm. Right atrial pacing was defined as normal ventricular contraction for subsequent comparisons. All succeeding ventricular pacing studies were then done with sequential pacing at an A-V delay of 20 ms. This pacing delay prevented ventricular fusion beats from contaminating the ventricular pacing effects of CRT. Contraction dyssynchrony was created by simultaneous RA and high RV free-wall pacing, which induced a LBBB-like contraction pattern. We chose to simultaneously pace at either the LV apex or posterior-lateral LV free-wall at the mid-ventricular level below the left circumflex artery to mimic CRT, referred to as CRTa and CRTfw, respectively. The order of apical and free-wall pacing was alternated among sequential animals to eliminate any sequencing effects. Pacing was sustained for > 30 seconds before measurements were made for each step so that hemodynamic equilibrium could be established. In practice, hemodynamic stability usually took < 15 seconds to occur. Between each ventricular-paced rhythm interval, the animals were returned to RA pacing and all hemodynamic variables were stabilized to baseline levels before the next step in the protocol was initiated.

Sonomicrometric and electrocardiographic data were recorded simultaneously using a software package provided by Sonometrics Corp. Three dimensional crystal positions time series were reconstructed from the raw data using the SonoSOFT™ Version 3.4.41 software provided by the manufacturer. All measurements were made with respirations suspended at end-expiration of 5 cm H₂O PEEP to control for the effects of cardiopulmonary interactions.

Orthogonal distance regression

To perform robust identification of the ventricular longitudinal axis direction based on all available data, we performed an orthogonal distance regression fit of a suitably constrained ellipsoid to each time frame of available position data. A general ellipsoid is described by the length of its three axes, the position of its center, and its orientation in space, for a total of 9 free parameters. To obtain the solution to the orthogonal distance regression problem, the sum of squared orthogonal distances of the individual data points to the parametrized shape is minimized for each timeframe. Statistically, this corresponds to a maximum likelihood estimate for the shape parameters under the assumption of independent, radially symmetric multivariate normal distributions of position measurement errors. The actual computation of the orthogonal regression solution is complex since the orthogonal distance of a given point to a parametric surface, such as the general ellipsoid, is not available in closed form, but can be formulated as the solution of two nested nonlinear programming problems (1). We implemented the corresponding algorithm in the MATLAB™ programming language and provide mathematical details of our implementation in the Appendix. The developed software is available under an open source license through this publication.

Choice of ellipsoidal model and constraints

We chose the parametric ellipsoidal shape because it captures key features of ventricular shape while making explicit the assumption implicit in the definition of LV twist.

Specifically, its longitudinal axis naturally defines a reference axis with respect to which rotational deformation is naturally described in the ellipsoid's internal coordinate system. Ellipsoidal models of ventricular shape have previously been used to assess the dynamics of ventricular geometry and to identify the ventricular longitudinal axis in cardiac positron emission tomography (10; 39; 41). The ellipsoidal shape can additionally be constrained by available additional information, such as the known apical placement of a specific marker. If the objective is accurate twist quantification, then the minor axes may also be constrained to be of equal length to avoid distortion of twist estimates by irregular radial contraction. A fully general tri-axial ellipsoid might be more suitable for accurate volume estimation and quantification of deviations from rotational symmetry if a sufficient number of measurement sites are available. While our software implementation supports all these possible variations, we report details only on results obtained by constraining the longitudinal axis to pass through a pre-specified apical crystal and forcing the two semi-major axes to be of equal length.

Twist quantification

The orthogonal distance regression was performed for each separate time-frame, using the estimation results of the previous time frame as initial guesses for the nonlinear optimization procedure. Thus, we obtained a time series of the nine ellipsoid parameters, which is then subjected to further analysis. First one verifies that a stable fit has been obtained, such that the solution varies continuously with time, then the position of the point on the ellipsoid surface closest to each measurement site yields natural coordinates for twist quantification (Figures 1 & 2) in which the relative angular movements of the measurement sites as a function of their longitudinal position can be examined directly. To analyze twist development over time, angular positions were expressed relative to a reference measurement site in a basal location and to the end-diastolic time point, defined as the pacing spike in the electrocardiogram for ventricular pacing modes and the QRS spike in RA pacing. To estimate global torsion, we performed a linear regression of radial angle on longitudinal position (described either as longitudinal angle ϕ or spatial position along the longitudinal axis), resulting in either the radial angle change per longitudinal angle change or unit distance along the longitudinal axis, respectively (4). Again, using the electrocardiogram to identify end-diastolic time points, the recorded cardiac cycles were separated and averaged for each pacing mode and subject. From these twist time-series, we computed twist amplitude, maximal rate of twisting, maximal rate of untwisting, as well as the twist acceleration (2nd temporal derivative) in absolute values and relative to RA pacing to summarize the data quantitatively. To reduce noise for derivative computations, a moving average filter with 5 samples window length was applied to the data before computing finite difference approximations to derivatives.

Visualization

To allow the investigator to interactively assess the output of the nonlinear regression procedure, movies of 3D representations of the “best fit” ellipsoid in relation to the positions of the measurement sites were generated.

Results

Test dataset acquisition & processing

We recorded 6-9 heart cycles for each pacing mode and subject for all five animals. Without tuning algorithm parameters or excluding data or manually pre-selecting any data, stable orthogonal distance regression fits for twist analysis (longitudinal axis constrained to pass through crystal positioned at apex, semi-major axes constrained to be of equal length) could be obtained for 4 of the 5 animals. The lack of fit stability in animal 2 is immediately

apparent from the tracings in Fig. 2, panel 2. While the fit can be stabilized by excluding particularly aberrant individual crystals, we chose not to do so to provide a report of pure automated method performance and exclude animal 2 for the purposes of further data analysis.

Orthogonal distance regression

The orthogonal distance regression procedure obtained excellent fits for all individual timepoints, with the median individual distance of the measured crystal positions to the optimal ellipsoid across all timepoints below 2.5 mm in 18 of the 20 animal/pacing mode combinations investigated. The largest median deviation was 3.1 mm in CRTa in animal 2, for which the fit proved unstable, anyways. The ability of the linear model for global twist quantification to describe the relationship between longitudinal position and local torsion varied from animal to animal, attaining significant p values in animals 3-5 with the exception of RARV pacing mode in animal 5. Animal 1, for which the estimation of the ellipsoid also proved stable, showed median p values of 0.08, 0.06, 0.52, and 0.19, for RA, RA-RV, CRTa, and CRTfw pacing modes, respectively, which may be due to the fact that we observed little consistent angular displacement of crystal positions in this animal.

Additionally, experiments where the linear global twist model did not attain statistical significance for the time point of maximal torsions are represented as dashed lines in Fig. 2. Representative frames illustrating the temporal development of the ellipsoidal fit, as well as the linear global twist model during the cardiac cycle are presented for representative animals 1 and 3 in Fig. 3. Note that while the ellipsoidal model fit both datasets quite well, the quantification of global twist based on a linearity assumption appears questionable for animal 1, but not for animal 3, where quality of fit was good in both respects, as is evident from the P values in Table 1 as well. For a more dynamic and comprehensive view of these time series data, the reader is referred to the videos provided in the online supplement (Suppl. 1 & 2), which allow to compare dynamical ventricular rotational deformation in all pacing modes simultaneously.

Comparison of global ventricular twist results between animals and pacing modes

All animals showed a clear initial untwisting at the beginning of systole in RARV pacing, potentially indicating that the untwisting had not been completed during the previous heart cycle. This phenomenon was essentially absent in RA pacing and clearly present in the biventricular pacing modes only in animal 5. Maximal torsion was lower in RA-RV than in RA in 3 of 4 animals. Maximal torsion was achieved later during the cardiac cycle in RA-RV pacing than in RA or CRTfw pacing regimes in all animals (Fig. 2), and later than CRTa in 3 of 4 animals. Maximal rate of torsion decrease in the untwisting phase was found to be lower in RA-RV pacing than in RA pacing in 3 of the 4 animals, but did not appear to be recovered in either CRTfw or CRTa except with CRTfw in one animal.

Discussion

Performance and comparison to existing approaches for twist analysis from low density data

The proposed analysis method appears to perform well on noisy data with irregular placement of a small number of measurement sites that would prevent application of previously described approaches (3), suggesting that it may be useful in lowering experimental requirements for twist quantification. The method allows to readily identify when data deviates significantly from a linear model for global twist quantification, an advantage on methods that rely exclusively on rotation quantification in individual planes that is shared with the cylindrical coordinate transformation technique described in (4).

Furthermore, the proposed methodology is theoretically attractive since it incorporates information from all available measurement sites in a fashion robust to noise. This is achieved by performing a maximum likelihood estimate of parameters describing a physiologically reasonable model that makes the assumptions underlying the analysis explicit. If unstable fitting results are obtained, that is, a discontinuous time series of ellipsoid parameters is obtained, this may be indicative of the possibility of several different fits to the data corresponding to local minima of the nonlinear objective function and may serve as a warning that marker data are inaccurate or too sparse, leading to an ill posed inverse problem (58). The researcher can then choose to either enforce fit stability by introducing additional physiologically motivated constraints, or exclude measurement sites suspected to be unreliable.

With regard to the quantitative interpretation of the ventricular dimension estimates obtained from the ellipsoidal fitting procedure, we observed that whenever a stable fit was obtained (animal 1, 3, 4 and 5), the horizontal axis length appeared quite well constrained by the data. The data are much less informative with respect to the length of the longitudinal axes, resulting in quite diverse length estimates. This is explained by the fact that in our truncated ellipsoidal model, the primary effect of differing longitudinal axis length is a change of ventricular wall curvature, with regard to which only 10 measurement sites are insufficiently informative.

A potential advantage of the proposed method over those described above (8; 15; 52) is that the data from all measurement sites can be taken into account when estimating the position of the rotation reference axis. This removes the requirement of placing measurement sites in parallel or even planar arrangement and should make results more robust to variations in measurement site location. If sufficient data are available, the constraint of forcing the longitudinal axis to pass through any particular (apical) crystal can also be removed, which, in the case of our test dataset led to stable ellipsoid fits in only 2 of 5 animals (data not shown), indicating that more position data is required for this approach to work reliably.

A clear disadvantage of our method is the computational expense. We would contend, however, that this is a minor disadvantage in view of today's ubiquitous availability of affordable computer resources. Finally, more detailed models of ventricular shape than the simple ellipsoid have been developed for various applications (9; 27; 53; 55). However, the constrained ellipsoid may represent the ideal level of abstraction for global twist quantification since it appears as one of the simplest parametric shapes with the required symmetries that can match ventricular shape data reasonably well and can be estimated from sparse data.

Evaluation of analysis results in test data set

The observation of delayed attainment of maximal systolic twist and reduced diastolic untwisting rate in the majority of animals in RA-RV pacing is consistent with previously published data (30). The shape of the computed twist time-series qualitatively agrees with previously published data derived both from radiographic twist quantification and gyroscopic measurements of apical torsion angle (30). Furthermore, the amplitude of total twist under baseline (RA) conditions agrees well with the methodologically most similar study (4). The lack of restoration of normal twist patterns with biventricular pacing supports previous observations when using a basal LV pacing site (47). However, this lack of normalization of twist with CRTfw or CRTa remains inconclusive due to the small sample size and resulting lack of statistical power, the acute nature of the open chest and open pericardium preparation, which may well affect ventricular mechanics, as well as the lack of independent physiological measurements in our test dataset that would support effective resynchronization. The lack of significant recovery of diastolic untwisting rate with

biventricular pacing suggests that the more rapid attainment of maximal twist, with consequent earlier, rather than more rapid, untwisting may play a role in improvement of LV function during CRT.

Possible extensions of this methodology

The potential exists that the proposed methodology could be used to compute time-series of other ventricular shape parameters, such as the deviation from circular symmetry in the horizontal plane. This can be achieved relatively easily by removing the constraint forcing both short axes to have equal length that we imposed for twist analysis, but does require data that is informative with regard to ventricular horizontal shape to achieve stable fits, that is that the markers need to be distributed around the ventricular circumference. In our test data set, stable fits for the more general scenario could be achieved only for 2 of 5 animals without intervention (data not shown). Approximations of ventricular volume from the best-fit ellipsoid truncated at the most basal crystal is also straightforward, but will require assumptions about exact depth of marker insertion and temporal evolution of ventricular wall thickness.

Limitations and future work

The computational performance of the current implementation does not permit a real-time visualization. This should, however, be achievable by implementing the proposed algorithm in a compiled language and performing further algorithmic optimizations, such as initializing the nonlinear program with a first, quickly computable best-fit ellipsoid with respect to algebraic distance (26). The algorithm can be used to quantify global twist from data derived from any measurement method that allows to track ventricular wall tissue sites, such as tagged MRI (without specific radial tagging), in the context of which such fitting techniques have already been applied, but might prove particularly useful to quantify twist from 3D speckle tracking echocardiographic data with its limited spatial and temporal resolution (7; 17; 31). In such data rich situations, removing the longitudinal axis constraint should be possible without loss of fit stability, yielding a fully automated twist quantification procedure. A crucial improvement of the proposed methodology, which will further extend its capability to operate in an unsupervised fashion, will be the full quantification of estimation uncertainty resulting from propagation of measurement error, model misfit, and ill-posedness of the inverse problem. This can, in settings such as this where multimodality is a possibility, be achieved by using Monte Carlo techniques, which we have shown to be, in principle, compatible with real-time operation even when applied to more complex models of physiology (57; 58). Transferring this approach to cardiac motion estimation from various data sources is currently work in progress. We acknowledge that conclusions regarding the physiology of CRT drawn from the analysis presented in this study are limited by the small sample size as well as the fact that we did not obtain external validation of the estimates of twist and torsion. However, using this same model and protocol we quantified the impact of dyssynchrony and CRT on torsion using speckle tracking echocardiography but without paired ultrasonic crystals (24). Consistent with our observations in this study, those data demonstrate that RA-RV pacing reduces torsion compared to RA pacing and that CRT partially restores it.

Conclusion

We describe a novel approach to quantifying ventricular twist from sparse, noisy time-series measurements of LV wall position, as typically results from sonomicrometric or radiographic measurement techniques. This approach, by explicitly modeling previously implicit assumptions, may be more robust to the presence of noise, irregularities in measurement site selection, and aberrant ventricular contraction patterns than existing techniques, and may reduce the number of measurement sites required to obtain meaningful

results. With input data of sufficient quality, analysis can be fully automated, avoiding any potential subjectivity that might bias analysis results, while input data of insufficient quality will lead visually and statistically identifiable failure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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APPENDIX: Methodological details of orthogonal distance regression procedure

We describe the algorithmic approach we implemented to fit a general or constrained ellipsoid to sparse data in an orthogonal least squares sense. Such a general ellipsoid is parametrized by the length of its three axes, the position of its center, and its orientation in space, for a total of 9 free parameters. The underlying idea is to perform two nested iterative optimization procedures: in the inner iteration, the distances of all points to the currently proposed ellipsoid are computed, while in the outer iteration, the ellipsoid parameters are adjusted to minimize the sum of squares of these distances to obtain a maximum likelihood estimate under the aforementioned assumptions.

Inner iteration: distance of arbitrary points to a general triaxial ellipsoid and its gradient

A triaxial ellipsoid surface in axis aligned position, centered at the origin in three-dimensional Euclidean space, can be described by the parametric equations

$$\vec{x}(\theta, \varphi) := \begin{pmatrix} a_1 \cos\varphi \cos\theta \\ a_2 \cos\varphi \sin\theta \\ a_3 \sin\varphi \end{pmatrix} \quad 1$$

where a_1 , a_2 , and a_3 denote the half length of the three orthogonal principal axes of the ellipsoid, while φ denotes the longitudinal angle and θ the rotation angle in the terminology of figure 1. Since our objective is to compute rotation relative to one of the ellipsoid axes, we will choose to align the longitudinal axis of the heart with the axis represented by a_3 in the above parametrization, so that θ directly relates to rotation about this axis. A necessary condition for some point $\vec{x}$ on the ellipsoid surface to be closest in the orthogonal distance

sense to a given point $\vec{p} = \begin{pmatrix} p_1 \\ p_2 \\ p_3 \end{pmatrix}$ is that the difference vector $\vec{p} - \vec{x}$ connecting the 2 points be orthogonal to the tangent plane of the ellipsoid at $\vec{x}$

$$(\vec{p} - \vec{x}(\theta, \varphi)) \cdot \frac{\partial \vec{x}(\theta, \varphi)}{\partial \theta} = 0, \quad (\vec{p} - \vec{x}(\theta, \varphi)) \cdot \frac{\partial \vec{x}(\theta, \varphi)}{\partial \varphi} = 0 \quad 2$$

which yields 2 nonlinear equations in the unknown angles θ and φ describing the position of points on the surface of the ellipsoid where the difference vector is orthogonal to the tangent

plane. While these equations cannot be solved in closed form and will usually not have unique solution, they can easily be solved numerically. As suggested in (37), convergence of a local optimization method such as Newton's method to the desired minimum distance solution, $(\vartheta_{\min}, \varphi_{\min})$ can be ensured in practice by using

$$(\vartheta_0, \varphi_0) = \left(\text{atan2}(a_1 p_1, a_2 p_2), \text{atan2}\left(p_3, a_3 \sqrt{\left(\frac{p_1}{a_1}\right)^2 + \left(\frac{p_2}{a_2}\right)^2}\right) \right),$$

that is, an initial guess in the correct "octant". Once the minimum distance solution has been computed, the actual orthogonal distance is simply $\|\vec{x}(\vartheta_{\min}, \varphi_{\min}) - \vec{p}\|$.

For robust performance of the overall method, we need to be able to compute the matrix of partial derivatives (the Jacobian) of the minimum distance solution with respect to the axes lengths a_1 , a_2 , and a_3 and the coordinates of $\vec{p}$ since these will be required by the outer iteration to make progress (approximation by finite differences would be feasible, but costly and potentially numerically unstable in this nested iteration setting). Fortunately, these 12 partial derivatives can be computed directly once $(\vartheta_{\min}, \varphi_{\min})$ are known by solving the system of 12 linear equations obtained when differentiating the necessary conditions (2) with respect to axes lengths and $\vec{p}$ – coordinates. For the resulting formulas obtained using the Maple™ 11 computer algebra system (Maplesoft, Waterloo, Ontario, Canada), the reader is referred to the computer code in the online supplement. The gradient of the distance is then simply obtained by applying the chain rule. We have thus described how to compute distances of arbitrary points to a centered, axis aligned ellipsoid.

Points in the original coordinate system where measurements were obtained are transformed into a coordinate system where the ellipsoid is centered and axis aligned. Such a coordinate transformation, consisting of the composition of a general translation and rotation, is given by $\vec{p}(\vec{p}) = T(\vec{p}) = R(\Psi_1, \Psi_2, \Psi_3)(\vec{p} - \vec{c})$, where $RR(\Psi_1, \Psi_2, \Psi_3)$ is in a matrix in the special orthogonal group SO_3 , which we chose to parametrize using a "yaw-pitch-roll" convention where the angles Ψ_1, Ψ_2 , and Ψ_3 denote subsequent rotations about the x, y, and z-axis, respectively, while $\vec{c}$ denotes the position of the ellipsoid center which is thus translated into the origin. This transformation is isometric and thus preserves distances, allowing us to compute the orthogonal distances $d(\vec{p}, a_1, a_2, a_3, \vec{c}, \Psi_1, \Psi_2, \Psi_3)$ of an arbitrary point $\vec{p}$ to an ellipsoid in general position parametrized by $a_1, a_2, a_3, \vec{c}, \Psi_1, \Psi_2$ and Ψ_3 . Since the Jacobian of T with respect to the angles is computed in a straightforward fashion, application of the chain rule allows us to compute the gradient of the orthogonal distance of a given point with respect to ellipsoid position, orientation, and half-axes lengths. The solution of the system of nonlinear equations (2) is obtained using the Gauss-Newton non-linear least squares algorithm as implemented in the *lsqnonlin* function in MATLAB 14 Optimization Toolbox.

Outer iteration and constraints

Given a set of measurement site positions $\{\vec{p}_1, \vec{p}_2, \dots, \vec{p}_N\}$, the optimization problem to be solved in the outer iteration is

$$\underset{a_1, a_2, a_3, \vec{c}, \Psi_1, \Psi_2, \Psi_3}{\text{argmin}} \sum_{i=1}^n d(\vec{p}_i, a_1, a_2, a_3, \vec{c}, \Psi_1, \Psi_2, \Psi_3)^2$$

which is a nonlinear least squares problem which is solved in a straightforward manner using any least squares solver once the inner iteration including derivative computations is

implemented. Numerical solution was accomplished using the Trust Region/Preconditioned Gradient method as implemented in the *fmincon* function in MATLAB 14 Optimization Toolbox.

To prevent convergence of the nonlinear program to degenerate solutions without influencing the optimization results, we constrained the axes lengths to be positive and smaller than three times the maximal distance between any basal and the apical measurement site for the longitudinal and twice the maximal distance between mid-plane measurement sites, respectively. Orientation angles were constrained to $\left[-\frac{\pi}{4}, \frac{\pi}{4}\right]$ for ψ_1 and ψ_2 , and to $\left[-\frac{\pi}{2}, \frac{\pi}{2}\right]$ for ψ_3 .

From the general fitting procedure outlined above, enforcement of equal length non-longitudinal axes is trivially obtained by eliminating one of the optimization variables and letting the other determine both values, thus reducing the optimization problem dimension by one variable. To constrain the solutions to ellipsoids with the longitudinal axis passing through a specific measurement site, we exploit that two of the three orientation angles can be computed from the constraint and the third angle, which remains an optimization variable, using simple trigonometric identities, thus reducing the optimization problem dimension by another two variables. For further implementation details, the reader is referred to the computer program available in the electronic supplement.

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Figure 1.

Sketch of the internal ellipsoid coordinate system. Longitudinal angles ϕ increase from apex to base, rotational angles θ increase in counterclockwise direction when viewed from the apex.

Figure 2.

EKG from the first analyzed cycle, torsion, and rate of change of torsion as a function of time, averaged over the available cardiac cycles. Dashed lines indicate datasets where the linear global twist model did not attain statistical significance (see Table 1 for an overview of fit quality measures). For dog 2, no stable ellipsoid fit was obtained without manual intervention, as is evident from the jump discontinuities in the plots. Note that the EKG deflections between 0.2 and 0.3 s in RA pacing in animals 3, 4, and 5 correspond to the atrial pacemaker spike in spite of their QRS-like morphology.

Figure 3.

Snapshots of end-diastolic time points (A, C) and maximal torsion time points (B, D) for 2 example experiments (Panels A,B: Dog 1, mode CRTa, Panels C, D: Dog 3, Mode RARV). In both cases, a stable ellipsoid fit was achieved, with the animal 1 data constituting an example of a “high curvature, short longitudinal axis” solution, while animal 3 shows an example of a “low curvature, long longitudinal axis” solution. CRTa pacing in animal 1 shows an example where the linear global twist model does not describe the relative rotational behavior of the measurement sites well, possibly due to the fact that there is little consistent angular displacement in this case, while it captures rotational behavior in RARV pacing in animal 3 quite well, as is evident from the bottom right subpanels, which show the projected crystal positions in internal ellipsoidal coordinates. Top panels show EKG with a green line indicating the snapshot’s temporal position. Coordinates for all 3D plots are transformed to position the most basal crystal in the xy-plane and align the longitudinal axis of the estimated ellipsoid with the z- axis. Green crosses indicate crystal positions, red circles the corresponding closest point on the ellipsoid surface, and green lines the orthogonal distance vector. The XY-perspective is seen from the apex. Please refer to videos 1 & 2 for an animated view of these experiments, with all pacing modes shown simultaneously for direct comparison.

Table 1

Measures of quality of fit of ellipsoidal model to crystal positions and of linear model for longitudinal position dependence of rotation (twist) for all animals and pacing modes. For details regarding the data presented, please refer to the manuscript main text.

Pacing Mode	Heart cycles	Total sum of all crystal deviations squared [mm ²] [†]	Individual crystal deviation [mm] ^{**†}	Ellipsoid horizontal longitudinal axis [mm] [†]	Ellipsoid horizontal axes [mm] [†]	R for linear correlation $\Delta\theta/\phi$ at point of maximal torsion [‡]	p [‡]
<i>Dog 1</i>							
RA	8	9.7 (3.5 - 12.9)	0.6 (0.0 - 2.5)	35.6 (33.9 - 39.0)	22.7 (21.6 - 23.9)	0.61 (0.59 - 0.63)	0.08 (0.07 - 0.09)
RA-RV	8	11.1 (4.9 - 13.2)	0.6 (0.0 - 2.5)	35.6 (34.1 - 39.4)	22.7 (21.7 - 24.0)	0.65 (0.64 - 0.65)	0.06 (0.06 - 0.06)
CRTa	8	10.9 (8.8 - 16.6)	0.6 (0.0 - 2.7)	37.9 (34.8 - 40.0)	23.8 (22.8 - 24.6)	0.25 (0.24 - 0.28)	0.52 (0.47 - 0.52)
CRTfw	8	10.4 (8.8 - 16.9)	0.7 (0.0 - 2.9)	38.4 (35.7 - 40.2)	24.0 (23.0 - 24.6)	0.48 (0.48 - 0.49)	0.19 (0.18 - 0.19)
<i>Dog 2</i>							
RA	6	91.0 (72.0 - 180.4)	1.6 (0.0 - 6.8)	17.8 (16.5 - 29.9)	30.5 (17.4 - 32.6)	0.31 (0.31 - 0.31)	0.42 (0.42 - 0.42)
RA-RV	5	122.6 (95.3 - 216.7)	3.0 (0.0 - 8.2)	25.5 (16.2 - 35.3)	19.1 (16.5 - 32.2)	0.24 (0.23 - 0.24)	0.54 (0.54 - 0.54)
CRTa	4	119.4 (81.2 - 189.7)	3.1 (0.0 - 7.0)	23.0 (16.4 - 35.7)	19.7 (16.3 - 32.6)	0.30 (0.30 - 0.30)	0.43 (0.43 - 0.44)
CRTfw	6	104.1 (84.4 - 201.6)	1.4 (0.0 - 7.2)	16.9 (16.4 - 33.4)	30.8 (16.4 - 32.3)	0.22 (0.22 - 0.22)	0.56 (0.56 - 0.57)
<i>Dog 3</i>							
RA	7	93.1 (72.2 - 116.4)	1.9 (0.0 - 6.3)	67.9 (52.8 - 72.1)	27.0 (25.8 - 28.8)	0.92 (0.92 - 0.92)	<0.001
RA-RV	7	90.0 (74.2 - 104.6)	2.0 (0.0 - 6.3)	67.1 (55.9 - 76.7)	27.6 (26.3 - 28.4)	0.93 (0.93 - 0.93)	<0.001
CRTa	7	101.7 (76.7 - 114.6)	2.2 (0.0 - 6.5)	74.0 (56.1 - 79.8)	27.6 (26.1 - 28.9)	0.77 (0.76 - 0.78)	0.02 (0.01 - 0.02)
CRTfw	8	97.9 (80.9 - 108.7)	2.3 (0.2 - 6.4)	63.5 (55.3 - 71.9)	26.5 (25.7 - 27.1)	0.74 (0.73 - 0.75)	0.02 (0.02 - 0.02)
<i>Dog 4</i>							
RA	6	121.3 (104.4 - 136.3)	2.2 (0.0 - 7.8)	35.3 (34.6 - 36.7)	25.9 (24.7 - 27.5)	0.87 (0.87 - 0.88)	<0.005
RA-RV	6	124.7 (113.8 - 143.6)	2.3 (0.4 - 7.9)	35.5 (34.4 - 38.3)	26.0 (24.6 - 27.8)	0.95 (0.95 - 0.96)	<0.001
CRTa	7	121.7 (109.0 - 138.3)	2.4 (0.4 - 7.7)	36.0 (35.4 - 36.8)	26.2 (24.5 - 27.6)	0.92 (0.91 - 0.92)	<0.001
CRTfw	7	119.6 (107.0 - 140.1)	2.2 (0.4 - 7.9)	35.2 (33.4 - 36.8)	26.1 (24.3 - 27.3)	0.92 (0.91 - 0.92)	<0.001
<i>Dog 5</i>							
RA	8	84.8 (74.4 - 94.4)	2.0 (0.0 - 5.6)	86.0 (70.3 - 90.9)	26.9 (24.3 - 29.2)	0.79 (0.78 - 0.79)	0.01 (0.01 - 0.01)
RA-RV	9	91.4 (77.9 - 97.9)	2.1 (0.0 - 5.9)	87.2 (71.1 - 92.9)	27.6 (24.8 - 30.0)	0.62 (0.61 - 0.63)	0.07 (0.07 - 0.08)
CRTa	9	112.5 (96.8 - 140.3)	2.4 (0.0 - 7.6)	36.7 (31.7 - 45.4)	22.9 (21.2 - 25.6)	0.77 (0.76 - 0.77)	0.02 (0.01 - 0.02)
CRTfw	9	107.5 (91.8 - 135.4)	2.2 (0.0 - 7.3)	35.8 (33.1 - 41.7)	22.9 (21.0 - 24.5)	0.73 (0.73 - 0.74)	0.03 (0.02 - 0.03)

Where applicable, values are median (minimum – maximum) ,

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* =over all measurement sites,
/ timepoints,
* heart cycles.