



Reference range calculation for myocardial T1

Application Tip

Cardiac, myocardial T1, normal values, reference range

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Step-by-step recommendations for calculating a reference range for myocardial T1 (or any other imaging biomarker).

Introduction: Why a local reference range is needed

In general, myocardial T1 measurement is not yet *reproducible* (i.e. site to site). This is because of the design and operation of different manufacturers' MR equipment, acquisition pulse sequence variations, T1 map creation algorithm/fitting methods, user imaging in systole or diastole, whether motion correction is applied or not, ROI placement choice, whether a population subgroup is used, whether blood correction is used, patient body temperature, ...etc. Therefore [SCMR clinical consensus guidelines](#) recommend that clinical users must create their own local reference range:

"For native T1 and T2 mapping, local results should be benchmarked against published reported ranges, but a local reference range should be primarily used."

"If local reference ranges are not available for native T1 and T2 mapping, quantitative results should not be reported clinically."

This article helps you to do the calculations in a statistically valid way. For more details, see the following publication: [Reference range determination for imaging biomarkers: Myocardial T1. Higgins DM, Keeble C, Juli C, Dawson DK, Waterton JC. JMIR 2019 \(in press\).](#)

Step 1: Check your T1 data distribution

Check that your collection of myocardial T1 values from normal volunteers (or patients referred to MR without cardiac disease) is consistent with a Normal distribution. The Shapiro-Wilk test is recommended because it is accurate for small sample sizes (but other tests are available). Online Shapiro-Wilk test [calculators](#) might be considered. Check that the *calculated*

statistic W is higher than the *critical value of W* (at 5% significance level). If it is, the data are likely consistent with the Normal distribution, and you may continue (otherwise it is not correct to use the following calculations).

Step 2: Check for outliers

Plot your data using a box-and-whisker plot ([online](#), if you like). See if any outliers are visible. If outliers are seen, review these subjects' data. Was there a problem with the scan that day? Consider removing these data points from the collection of T1 values, particularly if the values are clinically implausible.

Step 3: Calculate a reference range with confidence intervals

A reference range contains 95% of the population. A series of calculations are presented in the linked spreadsheets which make the calculations for you. Confidence intervals around the reference interval limits show how precise the reference range limits are. This is important when considering whether patients' values can be confidently classed as "abnormal".

Prepared spreadsheet:

[Excel 2010+ spreadsheet \(download\)](#)

FAQ:

How many normal subjects do I need?

A minimum of 20 (after removing outliers). This will at least allow benchmarking against other reference ranges from elsewhere. However, confidence in the location of the reference range limits will be low. "Normal subjects" can be people referred to CMR without cardiac disease, or volunteers.

If you know the approximate reference range limits, and the expected value for diseased tissue, it is possible to calculate how many subjects are needed so that the confidence intervals around the reference range limits are narrow enough to allow confident classification of the diseased tissue value as "abnormal". To limit the confidence intervals of the range-limits to a proportion (p) of the reference range, the number of subjects (n) required is: $n = 3/p^2$. For example, to make the confidence intervals of the reference range limits each to one-quarter of the reference range, $n = 3/(0.25^2) = 48$ normal subjects.

How to I compare my local values against a reference range from another site?

Ideally a local reference range should be used. However, benchmarking local data against published reference ranges is possible and recommended.

1. Measure 20 subjects (after removal of outliers)
2. Check: minimum 18 subjects within the external reference range. If yes, external reference range can be locally adopted, at least provisionally. If no, go to step 3.
3. Measure another 20 subjects (after removal of outliers).
4. Check: minimum 18 of the new group within external reference range. If yes, external reference range can be locally adopted, at least provisionally. If no, the external reference range is probably not valid and a local reference range should be created (but you already have n=40 for a local reference range).

Summary

These instructions for calculating a reference range are refer to myocardial T1 measurement. However the approach is general and may be applied to other imaging biomarkers.

For more background, details on the calculations, and example reference ranges from other Philips MR user sites, see: [Reference range determination for imaging biomarkers: Myocardial T1](#). Higgins DM, Keeble C, Juli C, Dawson DK, Waterton JC. *JMRI* 2019 (in press).



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