

The use of Z-scores in paediatric cardiology

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ABSTRACT

Z-scores are a means of expressing the deviation of a given measurement from the size or age specific population mean. By taking account of growth or age, Z-scores are an excellent means of charting serial measurements in paediatric cardiological practice. They can be applied to echocardiographic measurements, blood pressure and patient growth, and thus may assist in clinical decision-making.

Keywords: Blood pressure, cardio Z, echocardiography, paediatric cardiology, Z-score

WHAT ARE Z-SCORES?

Measurements are an important part of clinical assessment in the practice of paediatric cardiology. At the most basic level this typically includes measurement of the child's weight, height and blood pressure at clinic visits. Echocardiographic assessment is integral to patient assessment in the majority of children and decisions with respect to surgery or catheter intervention are frequently based on echocardiographic findings. In adult practice, ultrasound measurements are often reported with respect to a single "normal range" but this approach is impossible in growing children because the normal range of measurements will be impacted by patient growth and / or patient age. Therefore, the interpretation of these measurements during childhood presents a unique challenge, in determining whether a given measurement is within the expected range. In addition, if a measurement deviates from normality it is necessary for the clinician to gauge the magnitude of such deviation.

An approach to the description of clinical and echocardiographic variables is to describe the measurement in terms of a Z-score. The Z-score describes how many standard deviations above or below a size or age-specific population mean a given measurement lies. This approach has major attractions in paediatric

cardiology and is increasingly being adopted. As an example, the left ventricle will become larger in all children as they grow. However, if a patient with chronic aortic or mitral valve regurgitation is being followed through serial assessment then clearly it is an abnormal and inappropriate dilation of the left ventricle that must be excluded. The use of Z-scores facilitates the detection of pathological increases in left ventricular dimensions, over and above that expected due to normal growth, by showing an increased Z-score over time.

Z-SCORES VERSUS CENTILES

Many paediatricians and paediatric cardiologists are familiar with centiles, particularly with regard to patient height and weight. The relationship between centiles and Z-scores, for a normally distributed parameter, is shown in Figure 1; the use of either means of expression assumes a normal distribution of the data.

DERIVATION OF Z-SCORES

A Z-score is defined as $z = \frac{(\chi - \mu)}{\sigma}$

where χ is the observed measurement, μ is the expected measurement (population mean) and σ is the standard deviation of the population. Thus, Z-scores above the population mean have a positive value and those below the population mean have a negative value. The Z-score value conveys the magnitude of deviation from the mean. For example, where the mean size of the aortic valve is 20mm, with a defined standard deviation of 3 mm, the Z-score of an aortic valve with annulus 14 mm is:

$$z = \frac{(14 - 20)}{3} = \frac{-6}{3} = -2$$

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Therefore, in order to calculate a Z-score one must define the mean for each body size point, and the corresponding standard deviation. These values have been derived in many separate studies, of varying sample sizes, [Table 1] and the word ‘allometry’ has been used since 1936 to describe the “relationship between changes in shape and overall size”.^[1] The determination of the ‘best-fit’ relationship relies upon finding the best mathematical fit for the data, and it has long been recognised that the correlation between size of body structure (e.g. heart valve) and surrogate marker of total body size (e.g. body surface area or weight) is rarely a simple linear one.^[2-4] In other words, structures do not tend to obey the relationship

$y = ax + b$ (where y is the measured structure, x is the marker of total body size, a is the scaling coefficient and b is a constant).

Instead, a much better fit is generally shown by more complex polynomial equations (e.g. $y=ax^3+bx^2+cx+d$) or by a power law relationship ($y=ax^b$, where a is the scaling factor, and b the scaling exponent).

Once a best fit relationship is defined, a standard deviation and mean can be derived at each body size point. It is important to note that the standard deviation may vary with body size, a property termed ‘heteroscedasticity’.

WHICH PATIENT FACTORS SHOULD BE CONSIDERED?

The question of which patient factors should be used to reflect overall body size has been addressed in recent published guidelines.^[5] For most measurements, the recommendation has been to calculate Z-scores with respect to patient body surface area rather than height or weight alone.^[4] Many formulas have been used to calculate body surface area including those of Boyd, Dubois and Dubois and Haycock, and it should be noted that there is considerable discrepancy in the values derived by each formula, particularly at low body size. Recent published guidance has recommended the use of the Haycock formula,^[6] but there is a strong argument that for a valid comparison the same BSA formula should be used as in the original reference study which was used to compute the Z-scores.

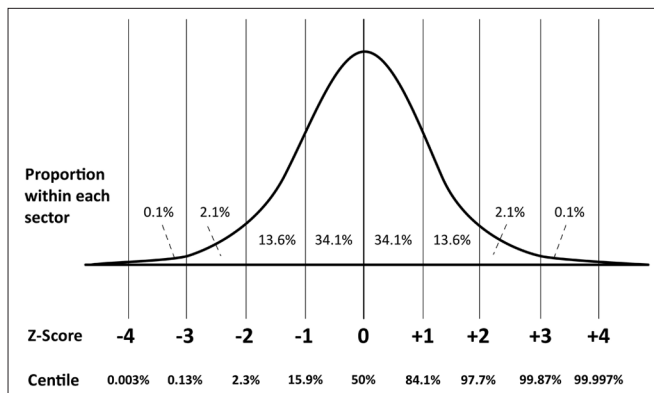


Figure 1: The relationship of Z-scores and centiles, assuming Normal distribution of the parameter. Note that the centile remains virtually constant at values distant from the mean (typically over 3 standard deviations from the mean), whilst the Z-score continues to be sensitive to changes in measurements

Table 1: Key references with respect to important paediatric and fetal echocardiographic data

Author	Year	Number of subjects	Parameters measured
Pettersen <i>et al</i> "Detroit" ^[12]	2008	782	Heart valves, aorta, pulmonary arteries, m-mode
Zilberman <i>et al</i> "Cincinnati" ^[13]	2005	748	Heart valves
Daubney <i>et al</i> "Wessex" ^[14]	1999	125	Heart valves and structures, aorta, pulmonary arteries
Kampmann <i>et al</i> ^[15]	2000	2036	M-mode measurements
Warren <i>et al</i> "Halifax" ^[16]	2006	317	Aorta
Gautier <i>et al</i> "Paris" ^[17]	2010	353	Aorta
Dallaire and Dahdah "Montreal" ^[18]	2011	1033	Coronary arteries
McCrindle <i>et al</i> "Boston" ^[19]	2007	221	Coronary arteries
Olivieri <i>et al</i> "Washington" ^[20]	2009	432	Coronary arteries
Schneider <i>et al</i> ^[21]	2005	130	Fetal heart valves and structures
Pasquini <i>et al</i> ^[22]	2007	221	Fetal aorta and duct
Cui <i>et al</i> ^[11]	2008	593	Time intervals from tissue doppler
Idem <i>et al</i> ^[10]	2004	325	Tissue doppler velocities, time intervals, pulsed wave doppler
Koestenberger <i>et al</i> ^[23]	2009	640	TAPSE
Fourth report ^[24]	2004	Meta-analysis	Blood pressures (Clinic setting)

TAPSE: Tricuspid annular plane systolic excursion

However, it should not be assumed that body surface area is always the favoured approach. For left ventricular mass, for example, patient height has been preferred.^[7-9] Other factors, such as patient sex and race, may also be important for certain measurements. Echocardiographic measurements do not simply relate to measurement of the size of heart structures. Normal values of functional data such as blood pool Doppler and tissue Doppler data also change across the paediatric age range, and are heavily influenced by patient age^[10,11] and heart rate.^[11]

APPLICATION OF Z-SCORES

In order to optimise the relevance of the computed Z-score in the clinical situation, the methodology used for the measurement should match, as far as possible, that of the original investigators.

In order for body surface area to be computed, conventionally both height and weight are required, and our normal practice has been to record both whenever possible. However, from experience, weight is recorded more commonly than height, particularly in smaller babies and children. Weight only equations for the calculation of BSA, such as $BSA = 0.1023 (\text{weight}^{0.68})^{[25]}$ are convenient but risk misappropriating the Z-score data. In addition, for some echocardiographic measurements there may be variability as to whether a measurement is made in systole or diastole or whether a leading edge to leading edge versus internal dimension method has been used.

One of the most useful applications of Z-scores is in tracking allometric growth over time. The same Z-score algorithm should be used each time, and a note made of which reference data has been employed. Z-scores may vary significantly between different authors [Figure 2]. If different Z-score references are used in the erroneous belief that these are interchangeable then an apparent change in Z-score may be produced in the absence of a true variation. In practice, an institution should decide which reference data is going to be used for which measurements and this should be used consistently during patient follow-up.

An example where z-scores can be very informative is

in following progressive dilation of the aortic root in a patient with Marfan's syndrome. The diameter at the sinuses of Valsalva will increase as the child grows, but at times of rapid total body growth it can be difficult to detect disproportionate growth of a single structure. Table 2 illustrates such a clinical scenario, where a child starts to grow rapidly at the age of 10 years. The aortic root grows even faster, and the significant increase in the Z-score of the sinuses of Valsalva demonstrates this succinctly and clearly, alerting the clinician.

LIMITATIONS OF Z-SCORES

Z-scores have major advantages for the presentation of paediatric echocardiographic and physiological data. However, Z-scores remain an imperfect approximation and there are some important drawbacks which merit discussion. The first, and most important, factor to bear in mind is that the mean and standard deviation at each body size point are only estimation and may vary widely between investigators [Figure 2].

Secondly, to have statistical confidence in both the mean and the more extreme Z-scores an extremely large sample size is required, particularly in the assessment of patients across a wide range of sizes. The change in variance across body size (heteroscedasticity) means that it is important to include sufficient numbers of patients at extremes of body size. The inappropriate averaging of variance would tend to underestimate Z-scores values for the smallest children, and overestimate Z-score values for the larger subjects.

Thirdly, the use of Z-scores may amplify errors in measurements. A degree of intra- and inter-observer variability in measurements is unavoidable, but Z-scores can amplify only minimal changes in absolute measurement [Figure 2b], particularly at negative Z-scores. The exact nature of any amplification effect depends upon the algorithm used to derive the Z-score, and some do not exhibit such a phenomenon.

Finally, it is important that the user does not accept published data uncritically. If there is a wide standard deviation for example in smaller patients, then a value of zero can appear to lie within 2 standard deviations of the mean. For instance, a complete absence of movement

Table 2: Increasing Z-score over time of the sinuses of Valsalva, suggesting pathological aortic root dilation

Age (years)	Height (cm)	Weight (kg)	Sinuses of Valsalva (mm)	Z-score (Detroit data ^[12])
7	125	23	25	+1.9
8	130	25	26	+2.0
9	135	28	28	+2.4
10	140	31	30	+2.4
11	150	35	32	+3.1
12	160	38	35	+3.7
13	170	41	40	+4.7

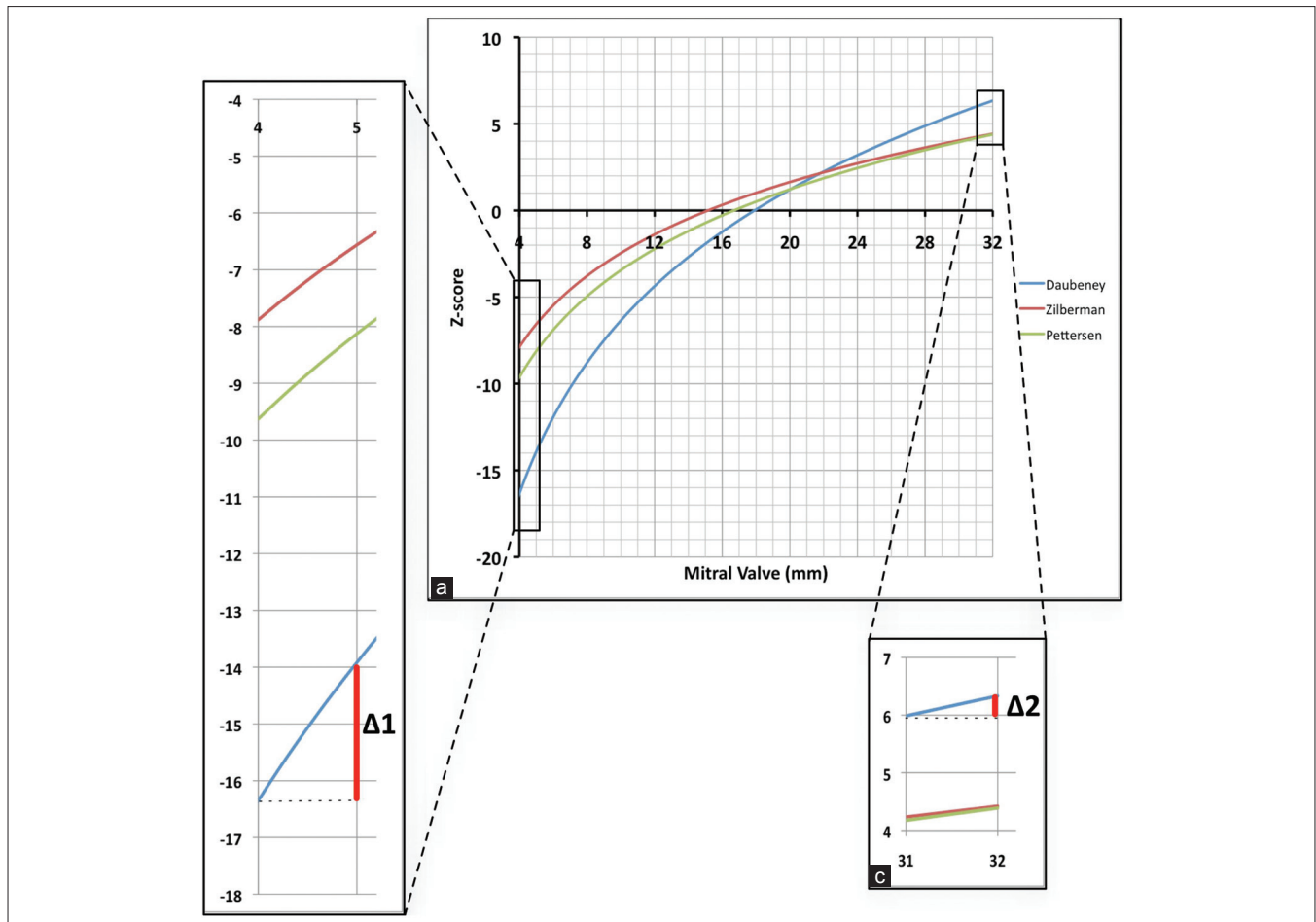


Figure 2: (a) demonstrates the relationship between mitral valve size in mm and the Z-score as derived by the three most commonly used algorithms. Values are calculated for a typical one year old male, weight 10kg, height 75 cm. The algorithms agree relatively closely around the mean (Z=0). (b) and (c). There is considerable discrepancy between the different algorithms, particularly at low Z-scores. $\Delta 1$ and $\Delta 2$ demonstrate the difference in magnitude of the change in Z-score, with a 1mm variation in measurement, at low and high Z-scores respectively

on tissue Doppler at some positions, in the under one year age group, may yield a Z-score of >-2 .^[10]

HOW TO CALCULATE Z-SCORES IN PRACTICE

For the clinician, it is impractical to trawl through multiple paper reference sources in a clinic setting. It is important, though, that there is the ability to calculate Z-scores when required and there are some commercially available echocardiography archive packages that facilitate this. Though convenient, these integrated packages are often limited to a single set of reference data and have not extended to the incorporation of functional data such as blood pool or tissue Doppler. Fetal echocardiographic data is available on some archive solutions and not others.

Some institutions do not have image archiving systems installed and so web-based calculators have evolved. Probably the best known of these is at www.parameterz.com, where the user can input the relevant data for online

calculation of Z-scores based on published reference data. Our own unit has recently released the “Cardio Z” App which can be installed on an iPhone/ipad platform and does not depend on an Internet connection. This permits user configuration of the preferred reference source for multiple fetal and paediatric echocardiographic measurements. The user has the option to change the body surface area formula, but the default position is to use that of the original reference. Diagrams detail the exact measurement methodology used by each paper, in order to facilitate valid comparisons with the reference data. Functional data, such as pulsed wave and tissue Doppler with derived functional indices, can also be entered. Supplementary information such as Z-scores for growth and blood pressure, and normal electrocardiographic data can also be analysed. A screenshot of the App is shown in Figure 3.

CONCLUSIONS

The use of Z-scores represents a helpful way of presenting



Figure 3: Main menu screenshot of the Cardio Z app showing the variables for which Z-scores can be calculated. The user can configure the reference data to be used and the formula to be used to calculate body surface area. The data can be stored as a “.pdf” document for emailing or storage

patient specific information in paediatric cardiology. Users need to have an awareness of how such scores are calculated and their limitations. Purpose-designed software is making access to Z-score information far easier than it was possible in the past.

DECLARATIONS

HC and JMS are the joint authors of Cardio Z, an App developed for iPhone and available for purchase. Profits from the App are used to maintain future development and are donated to the Evelina Children’s Hospital Appeal.

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Announcement

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