

Heart Valve Size Estimates Using Body Indices

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INTRODUCTION:

Indices of body measures are numerous for both humans and animals. Body Surface Area (BSA) estimation began for humans in the early 18th century. Investigators used three approaches in measuring BSA: coating, surface integration and triangulation. Research began on body measures for animals in the last half of the 18th century when energy consumption and conversion along with efficiency of gains became of interest in livestock production. Weights of animals were raised to fractional powers for these studies. DuBois & DuBois (1916) developed a very early model. Boyd, Scammon & Lawrence (1930) and Boyd & Scammon (1930) developed another model; followed by Boyd (1935) with yet another model. In mid-20th century Brody (1945) developed metabolic body size for cattle; this was modified slightly by Kleiber (1961). Selzer (1966) worked more on human BSA. Gehan & George (1970) and George & Gehan (1979) contributed more. Haycock (1978) added still more. Mosteller (1987) also added to the BSA literature. Pharmaceutical companies today use BSA for dosing assorted drugs. The DuBois formula seems to be the most widely known and used version. Oncology drugs are often dosed based on body surface area (BSA). The position being that dosing per unit of weight alone causes too large a dose for stronger medications.

Scaling between species was first researched in the 1990's. West, Brown & Enquist (1997 & 1999) began studying scaling, a recently invoked term used for inter-species studies, where results from, say, pigs may be extended to humans. Why scale? It may be useful to know selected biometric dimensions between mice and rats, between rats and dogs, between dogs and pigs? When new drugs are developed, these laboratory species are the first exposed. If the allomorphic relationships existing between species are known, it may well help scaling doses -- more accurately from mice to rats to dogs to pigs. It may ultimately help scale doses up from mice to humans? When toxic effects are determined, is there a relationship -- linear or otherwise -- between species? Does some mathematical relation between body size or organ size exist that will be helpful in dealing with the conundrum of drug effects -- beneficial or toxic?

In this study the idea was to confirm if possible -- recent reports from West, Brown & Enquist at the University of New Mexico and Los Alamos National Lab -- where areas of heart-valves scaled to the $3/4$ power of body mass (1997). West, Brown & Enquist (1999) also reported finding that heart valve diameters scaled to the $3/8$ power of body mass. The interest in this study was to be able to use body measures to estimate the diameters, radii or area of heart valves without the time-consuming and expensive harvesting and storage normally required.

To help execute this general plan, numerous body indices are available. Some of these have been in use since the mid-nineteenth century. At the time the primary interest was estimating energy consumption. Bomb calorimetry was expanded to facilitate measuring cattle in the early twentieth century -- searching for development of a body index, but mostly to estimate energy consumption. Early on these estimated growth. Are they useful to estimate heart valve size?

We all have heard efforts to get you to donate organs and other tissues. Donated tissues accumulate costs the moment tissues are volunteered: (1) There are the inevitable forms and records that must be completed and maintained, (2) There are harvesting costs, (3) Sanitation and sterilization costs (check with CryoLife) (4) Transportation costs (5) Storage costs (6) Inventory costs (7) More transportation costs to the recipient (8) Installation costs (9) Recuperation costs, to name a few. While tissue banks are mostly not-for-profit organizations, that does not mean they have unlimited resources. Next to maximizing sales, controlling costs are an well-accepted approach to conserving resources. If donated tissues can be estimated from outside the body -- without surgery (harvesting) -- considerable time, energy and costs can be saved, by deferring tissue or organs and not harvesting them in the first place. By knowing the most-required valve sizes we are on the road to saving money or conserving resources. Rejection (deferral) can be imposed without additional costs. It seems reasonable that some index may be useful in estimating heart valve sizes.

Two heart valves are of primary interest: Aortic and Pulmonary. Other valves are seldom harvested. Particular sizes of these valves are sought. Aortic valves with diameters of 25mm or larger are of premier interest. Pulmonary valves 20mm and smaller are most desired.

Elizabeth Boyd and co-workers in the 1930's published several papers (art cites). Important among her findings was an opinion that humans may not complete growth until around the age of 25. If she is right, age is a useful variable in estimating valve size.

"Growth curves" are generally sigmoid. There are two points of inflexion -- one soon after birth, another not too long before the curve "tops out" and reaches a long-term plateau (i.e., maturity). What is being said is that growth continues, but the rate typically undergoes major changes twice during the growth of an individual -- human or animal. Boyd says that humans "top out" about twenty-five years of age. It stands to reason that since males usually are larger -- height and weight -- their growth may continue longer than females.

Heart valves are typically not collected from individuals greater than 50 years of age. More evidence that age probably has impact on the valve size and usefulness. It is certainly reasonable that younger donors will provide valves that are more elastic and pliable. These are more adaptable for implantation.

Several authors have published works estimating Body Surface Area (BSA). Several others have published various other body indices. The Body Mass Index (BMI) has had recent interest in body size studies. BMI is also the measure used by some of the military services to estimate body size and body fat.

Two weight-only based body indices have been used: $\text{Body Weight}^{0.67}$ and $\text{Body Weight}^{0.75}$. Brody advanced the $\text{Body Weight}^{0.67}$ from work done in the eighteenth century. Kleiber began the argument for use of a $X/4$ power in the early twentieth century. The attributes these indices have are that both use only weight, and these can therefore be applied to animals.

The variables most frequently used in all of these studies are simply available: age, sex, height, weight. Connecting these with the aortic and pulmonary valves was the issue. Obviously, in animal work the height is not applicable; all other variables do apply.

METHODS:

This was step one of a two-step project: Preliminary modeling. Data was entered to develop a model for subsequent testing. Later after more data has been gathered, the model will be tested and adjusted further. In this phase of the project, we used as much data as possible, but with a rigid limit -- aortic valves were 25mm or greater. This, to get to an early and decent mathematical "fit" of the model.

A data set was imported from the sponsor. The data was cleaned and checked closely for consistency. Quite a bit of time and effort was spent getting the maximum information available for all entries. Heights and weights were especially important since these two variables enter in most body indices. Two valves donated by the same individual caused two records to be generated. These were consolidated for this purpose.

Age is indicated as AGER (AGE Revised: there were many units used [i.e., weeks of gestation, hours, days, weeks and months] since neonate valves had been collected. All age units were calculated but rounding was imposed to get to a reasonable decimal count. The minimum age was then restricted to 0.01 years. AGER then indicates AGE Revised to consistent units -- years.)

Bedrock steps started with Proc Corr(elation) to check the data set for relations between the variables. The next question was which are most closely related to which set of body summary variables? This then involved use of Proc Reg(ress). Various sets were compared using Corr and Reg.

It made no sense to allow more than one body index of any type to enter any set of solutions. The body measures themselves (i.e., age, sex, height, weight) were all entered and allowed to enter as many models as there were possibilities. Indices, whether body weight indices (weight alone to some fractional power) or body mass indices (i.e., weight, height and some constant taken to a fractional power) were restricted to a single entry per solution -- owing to the high degree of correlation between these computations that all used height, weight and some constant raised to fractional exponential powers.

RESULTS:

Preliminary information about the input data set (DEMOHART) is provided in Tables 1 and 2. Table 1 indicates the numbers and types of valves donated by males and females. Table 2 indicates means and summary statistics about the donors and their aortic valves summarized here. The variables summarized are AGER (yrs), height (BHCM, cm), weight (BWKG, kg), body mass index (formula), body mass raised to the 3/8th power (BDYMS375), Body Surface Area (BSADB_DB, DuBois & DuBois formula) and aortic diameter (AorDiam). Table 2 separates the sexes. While developing the "model" for valve prediction, close attention was paid to the Coefficient of Variation (CV). Attention is invited to the numbers of observations for males and females. This element has impact shortly. Height was the most frequently missing data element that caused NMiss to be so large throughout the study.

Table 3 looks only at aortic valve donors. The criteria for entry into the dataset (BIGAORTS) was an aortic diameter $\Rightarrow$ 25mm. The missing are accounted for by quarantined or discarded valves. Valves may have been harvested but were not "available for shipment".

Table 4A examines the same set of variables examined in Table 2, except that AORDiaPr (predicted aortic diameter) has been added. Dataset = BIGAORTS and is across genders. Note the small CV for the AORDiaPr.

Table 4B looks at the same dataset for the same variables, separated by gender. Small numbers of female aortic valves available. There is a serious issue of disproportionality between the two sexes in the dataset. This has further impact in upcoming tables. Again, note the CV's for AORDiaPR for males and females.

Table 5A is a Proc Corr output for the same data in Table 4A -- across sexes. Aortic diameter is provided as a baseline measure. Sex is negatively correlated with both AORDiam and AORDiaPr. Note, however, the size of the correlation for AORDiaPr with age and weight. Body Mass to the 3/8th power (BDYMS375) was slightly larger than the correlations of BDYMSIN and BSADB_DB, but not as strong as weight (BWKG).

Table 5B is a Proc Corr output for the same data in Table 4B -- by sex. AGER is the most highly correlated with AORDiaPr -- to a very substantial level. Other variables vary as to levels of correlation particularly with AORDiaPr. The different correlations of BSADB_DB with AORDiaPr between males and females is substantial, almost double. The small numbers of females in data=BIGAORTS is almost sufficient to end further discussion.

Figure 1 plots AGER and AorDiam (A = males, B = females). The 25mm diameter is provided as the horizontal reference. Dataset BIGAORTS is plotted.

Figure 2 plots BWKG and AorDiam (A = males, B = females). The 25mm diameter is the horizontal reference. BIGAORTS is plotted.

Figure 3 plots BDYMS375 and AorDiam (A = males, B = females). The 25mm diameter is the horizontal reference. BIGORTS is plotted.

Table 6 is the result of Proc Reg (stepwise). Table 6A output reflects age following the intercept, as the first variable entering the model in Step 1. Sex enters in Step 2. While not statistically significant, it was marginally significant ($0.05 < p < 0.10$), and it caused additional reduction in Mallow's C_p . This was probably a function of numbers between sexes. Table 6B is the same model run by sex. The female model had no variable satisfy entry criteria ($p < 0.15$). The male model again showed age entering the model after the intercept. Weight (BWKG) entered following age. The p-value for weight was not statistically significant, it did satisfy the entry criteria of $p < 0.15$.

Figure 4A is a plot of AORDiaPr vs AorDiam for all observations, which includes both sexes. Figure 4B is separated by sex. The male version illustrates a hint of linearity above the reference line (25mm aortic diameter).

FOLLOW-ON:

Soon after completion of this work, the model solution was set aside in part: A new database was not installed at the sponsor's facility as anticipated when the project began. Work continues using components of the model. Ages, weight and heights are used to "estimate" the likelihood of deferring the valves donated. Means $\pm$ two standard deviation units as measured for these three variables are used for the "estimate". Yes, these are yielding approximately 95% accuracy in estimation of keeping candidate valves.

When sufficient data is accumulated, the second phase will begin. If there are sufficiently more female records, the model will be revised to improve the fit for both sexes.

APPENDIX A: Setup and Computations

Data acquisition: Data was imported from a file provided by The Sponsor, Tissue Processing Group. These raw data were screened for completeness and consistency. Feedback from these checks was provided to the Tissue Processing Group, in the form of questions and notes to verify possible points of confusion. These included comparing and matching units within weights, heights and resolving units for ages especially of infants, where multiple units of age are frequently used: minutes, hours, days, weeks or months. When these updates were returned an updated file was prepared for model development.

Data Preparation: The raw data was modified for one variable: All ages and age units were recalculated to a consistent unit, years. As a result of this change, infants aged two days and younger were assigned values of 0.01 years. This action affected eight children in the 1180 observations (0.6 %) and was believed to have a trivial impact on the accuracy of the data, other than those under two days old. Those three days and older were converted to years using up to two decimal values in the result. The AGE variable was then renamed, age revised -- AGER. AGER was then subsequently used, throughout.

Several variables were converted from avoirdupois to metric units for use in various formulae. This was done since most body surface area and various body indices use metric measures for both weight and height. Details are below. A number of variables were calculated based on reports from various sources, using the transmitted file. These formulas were used for calculations:

Converting avoirdupois units to metric for subsequent calculations (CRC Handbook of Chemistry & Physics) :

$bwkg = wgtlb * 0.454$	rounded to 0.1
$bhcm = hgtin * 2.54$	rounded to 1.
$bwgm = bwkg * 1000$	rounded to 0.01
$bhm = bhcm * 0.01$	rounded to 0.01

Body Surface Area from various authors:

DuBois & DuBois	--bsadb_db = ((bwkg**0.425)*(bhcm**0.725)*(0.007184))
Gehan and George	--bsagh_gg = ((bwkg**0.51456)*(bhcm**0.42246)*(0.02350))
Haycock	--bsahayck = ((bwkg**0.5378)*(bhcm**0.3964)*(0.024265))
Mosteller	--bsamostr = ((bhcm*bwkg)/3600)**0.5

Body Size Indices from various sources:

Body Mass Index	--bdymsind = (bwkg/(bhm**2))	rounded to 0.01
Metab/c Body Size**0.67	--mtbdsz67 = (bwkg**0.67)	rounded to 0.01
Metab/c Body Size**0.75	--mtbdsz75 = (bwkg**0.75)	rounded to 0.01
Ponderal Index	--pondindx = (bhcm/(bwkg**0.33))	rounded to 0.01

NB: a single asterisk '*' indicates multiplication.
a double asterisk '**' indicates exponentiation.
a forward slant '/' indicates division.

These values, once calculated and converted were used throughout. A number of SAS System® data management tools were used including: Procs (procedures) Freq(uecy), Means, Univariate and Plot to better understand the data, locate the presence and position of outliers to see the ranges and limits of the variables.

APPENDIX B: Modeling Background

Modeling: Once the variables were calculated and reviewed for consistency. Several statistical procedures were used: Procs Corr(elation), G(eneral) L(inear) M(odels) and Reg(ression) particularly to produce a model for the Aortic diameter (AorDiam). Several statistics (i.e., minimums, maximums and coefficients of variation) calculated by the procedures were very helpful in developing the model. These statistics were useful in knowing the details and range of the raw data in use.

Proc Reg was the primary tool in the modeling, although Proc Corr was used heavily. The stepwise regression option was used to allow SAS to determine the relationships between several of the variables. One constraint was imposed -- that was keeping a relatively simple model, where a single type of BSA or body index was permitted to enter a solution. It made no sense to let both a BSA calculation and a body index serve as solutions. These BSA and body index variables were sufficiently complex and correlated such that the use of more than one seemed nonsensical.

When examining the output from the regression procedure, the reader is reminded of three important elements:

(1) Variables were permitted to enter the model if the probability value attached to their entry was less than $P \leq 0.1500$. There are notations on some of the tables provided indicating "no other variable met the 0.1500 significance level for entry into the model."

(2) If a variable satisfied (1) above, it was permitted to enter the model. As the variable entered the model, the 'Model R-square' term increased as a result of the inclusion. The 'Model R-square' term was recalculated as a function of the new term in the model. If the 'Model R-square' term did not increase, the variable was removed from the model.

(3) Simultaneously with (2) above, Mallow's C_p was calculated. Mallow's C_p was to reduce in magnitude with the addition of a term in the model. Again, if this criterion was not satisfied, the candidate-variable was removed from the solution.

These three criteria were simultaneously at work to provide a model. If a variable did not satisfy all three criteria, it was not permitted in the model. Or, if it had satisfied the criteria at one point, but not as a subsequent variable was 'presented' the first variable may have been removed.

The value of the early studies of the data (i.e., descriptive statistics, plots and correlations) provided in the report was that these variables examined were 'good candidates' for inclusion in a model. This is verifiable by the absence of terms removed from a model, once included.

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