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Ratiology and a Complementary Class of Metrics for Cardiovascular Investigations

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Cardiovascular investigations often involve ratio-based metrics or differences: ejection fraction, arterial pressure augmentation index, coronary fractional flow reserve, pulse pressure. Focusing on a single number (ratio or difference) implies that information is lost. The lost companions constitute a well-defined but thus far unrecognized class, having additive value, a physical dimension, and often a physiological meaning. Physiologists should play a prominent role in exploring these complementary avenues and also define alternatives.

Introduction to Markers and Metrics

Data collection is an important component of clinical research and the diagnostic process. Interpretation of all pieces gathered is the next step. In contrast to the evaluation of subjective findings (such as fatigue), it is often assumed that all measured and calculated quantities are unequivocally interpretable once their reference values are available. This notion may be true for body temperature, hematocrit, etc. However, often paired observations are considered, e.g., systolic and diastolic arterial blood pressure levels. Interpretation of such a data pair is not always a straightforward procedure, as illustrated by the regular congresses on this theme and the evolving discussions about how to best determine the two pressure readings. Alternative and additional routes for interpretation have been proposed, such as the analysis of mean arterial pressure (MAP), pulse pressure (PP), as well as other variants.

Clinically used metrics often serve as disease- or patient-oriented (bio)markers (6), meaning that they have been demonstrated to reliably predict an outcome. For example, end-systolic volume (ESV) index as determined during reperfusion therapy for acute myocardial infarction is a strong predictor of early and late mortality (56), an indicator for long-term survival after coronary artery bypass graft surgery (21), a sensitive marker of acute response to cardiac resynchronization therapy (7), the major determinant of survival after recovery from myocardial infarction (69), carries prognostic value in patients with asymptomatic aortic regurgitation when assessed during exercise (61) and serves as a predictor of heart failure hospitalization in stable coronary artery disease (55).

In a recent editorial comment on various indexes testing for coronary ischemia, including half a dozen ratios, Kern and Seto (46) raise the lapidary question "Are all things equal?" In their search for answers, the authors state: "How does one sort the numerous contenders in the field for best test when a gold standard, the demonstration of lesion-specific myocardial ischemia in humans, is wanting? We are obligated to accept a surrogate standard (e.g., nuclear perfusion imaging, PET, stress echocardiography) or accept a strong agreement to an index previously validated on the bench and in the clinic. Nonetheless, absent a true gold standard, the best intracoronary ischemic parameter will remain contentious." The present contribution does not solve all problems but offers a refreshing view to guide future studies in cardiophysiology as far as ratios are involved. A companion derived from the Pythagorean theorem (37) has a prominent role in this approach.

Why Ratiology?

The term *ratiology* is a neologism referring to the study, application, and interpretation of ratios. This newly introduced concept also covers peculiarities around the statistics of reciprocals, the invariance of the mandatory companion regarding selection of nominator and denominator, and interpretation in terms of clinical relevance, although not all of these aspects are covered in this prolegomenon. Applications of ratios in cardiophysiology systematically divide the smaller one of each pair by the larger, or the reverse. The selection implies that the outcome is always either ≤1.0 or ≥1.0, depending on the preferred choice. Ratios have been used either as a continuous scale (e.g., from 0 to 100%) or primarily as a specific level that is employed to define a cutoff value for pursuing intervention. How does this popular formulation in terms of an appealing fraction drive our worry about the interpretation of such ratios? Stated in plain words, the answer is: a ratio only considers the result of some kind of manipulation (in this case, the dividing operation) essentially to derive one number from paired measurements *X* and *Y* (FIGURE 1, TOP), without attention to the values of *X* and *Y* themselves. The same limitation applies to the process of subtraction or multiplication (43). In all cases, a single number emerges without thought about the portion of information that has disappeared. Here, we offer a convenient solution to this dilemma (FIGURE 2) and also seek to identify the impact of the lost companion (Table 1). We address three areas dominated by the use of ratios: ventricular pump (dys)function, coronary perfusion impairment, and evaluation of arterial blood pressure recordings. For each scenario, we explore the relationship between the corresponding building blocks *X* and *Y*, as well as the connection between their ratio and *Y* (FIGURE 3) or *X*.

Fractions and Percentages as Metrics

TV sets, smartphones, and computer monitors have a rather fixed ratio of screen width and height, often 16:9 for the widescreen type. Although this aspect appears to be rather universal, there is only one number in use to distinguish various screen sizes. This number refers to the diagonal size, often expressed in inches. In fact, the present paper is largely about diagonals, specifically as they are encountered in (graphical) analysis of data measured in the field of cardiology. As we will argue, every ratio is accompanied by a "diagonal," which often carries relevant information and therefore needs attention.

Not all ratios are of the same nature. In daily life, ratios come in various types of appearances. Many classes are characterized by physical dimensions, e.g., the peak velocity of a cyclist (as miles per hour, or converted to equivalent units such as meters per second) and fuel consumption of a Hummer (as miles per gallon). Other ratios carry no dimension and are just a number or percentage. For example, a stock market index is difficult to interpret if without further details on component companies' market capitalization, capping factor, free float, or knowing whether a weighted arithmetic mean is applied. Decreased to 50% is not always identical to decreased by 50%. Likewise, when a hotel offers a 5% discount, then it matters for the backpacker whether this concerns a five-star luxury resort or actually points to a youth hostel. Also, if the flat tax rate is 28%, then it will be tricky for a state official to discuss the annual budget as long as the average income per resident and the actual number of tax payers remain unknown. Furthermore, a ratio is not necessarily a constant over the full range encountered, even when a single category is looked at. Percentages expressing a rate may vary depending on the level that is considered, e.g., a tax rate may progressively increase for higher income groups.

Other types of ratios may offer a straightforward interpretation, namely if it is clear that one of the two underlying components is more or less constant. An example concerns fractional shortening of a sarcomere, where length at rest is somewhat fixed (mostly ranging from 1.9 to 2.2 μm), implying that, for the cardiomyocyte, the relative shortening is inversely and nearly linearly associated with final contraction length (30). Yet another category of dimensionless ratios with simple interpretation exists, namely those with an internally specified or "individual" reference, where ranges for values in numerator and denominator still may widely differ. A readily available and universally discussed example concerns relative finger length. The length of the index finger (D2) may largely vary among

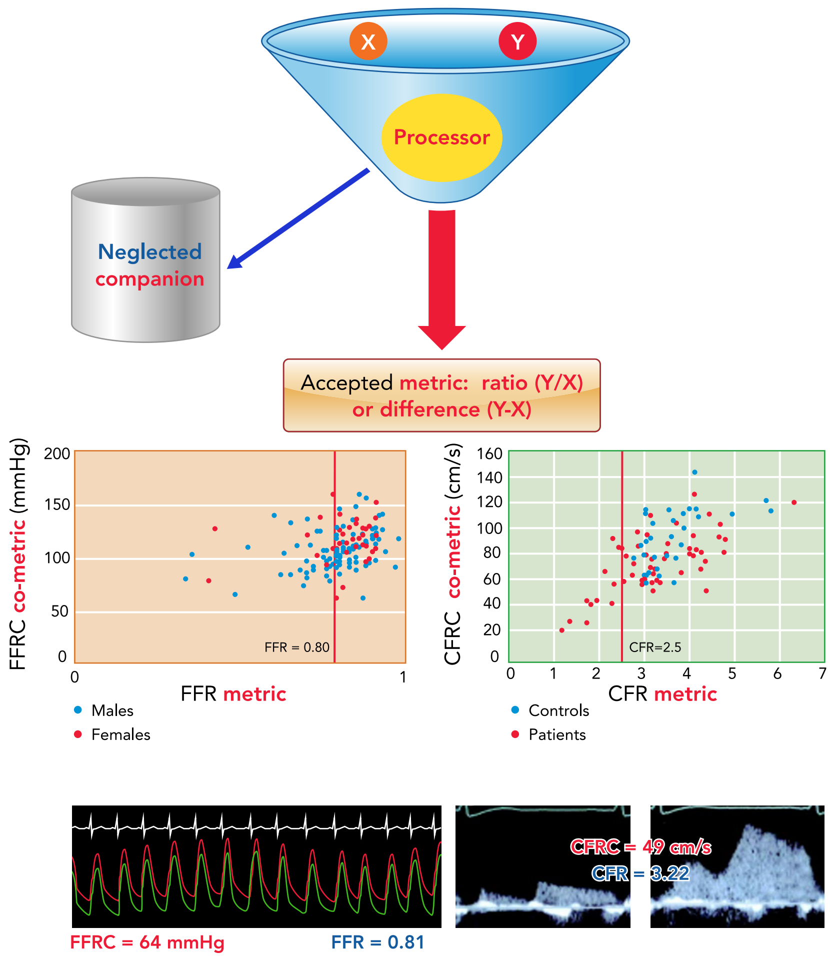

FIGURE 1. **Variables *X* and *Y* are processed to form a ratio (or difference) along with a newly defined companion (C)**
Recording examples (*bottom*) provide components for ratio-based approaches to study the coronary system, namely via fractional flow reserve (FFR) or coronary flow reserve (CFR). Our study introduces FFRC and CFRC to compensate for the limitations of the ratio-based metrics. Each companion refers to the associated hypotenuse, as further explained in the text. Cut-off levels for the companions require robust evaluation, and their future inclusion emphasizes that the ratio alone is insufficient to evaluate a patient in a personalized manner. Data are from Cardiovascular Center, OLV Clinic, Aalst, Belgium, and from the Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy.

Table 1. ***Current metrics based on a ratio or difference, along with their companions***

Metric or Companion (C)	Relevant Physiological Variable(s)	Relationship Permitting Identification	References
EF	Key variable **ESV**	EF (%) = $100[1 + (C_1 \cdot \text{ESV})/(C_2 + \text{ESV})]$	37, 38
EFC, ml	Preload (**EDV**)	EFC = 0.78 EDV + 12.4; R^2 = 0.982, N = 155	37
FFR (1)	Driving pressure (**Pd**)	FFR = 0.004 Pd + 0.53; R^2 = 0.350, N = 129	44
FFR (2)	Gradient (**Pa–Pd**)	FFR = –0.94(Pa–Pd) + 96.48; R^2 = 0.802, N = 129	44
FFRC, mmHg	**Pa**	FFRC = 0.725 Pa + 5.745; R^2 = 0.933, N = 129	44
CFR	Recruitable ΔDPV = **DPVh-DPVr**	CFR = 0.04(ΔDPV) + 1.21; R^2 = 0.721, N = 56	44
CFRC, cm/s	**DPVh**	CFRC = 0.99 DPVh + 3.69; R^2 = 0.993, N = 146	44
PP, mmHg	**SBP**	PP = 0.602 SBP–32.15; R^2 = 0.745, N = 146	45
PPC, mmHg (1a) children	MAP based on **SBP** and **DBP**	MAP = 0.42 PPC + 27.9; R^2 = 0.98, 46 groups (*)	45
PPC, mmHg (1b) adults	MAP based on **SBP** and **DBP**	MAP = 0.58 PPC + 8.4; R^2 = 0.95, N = 147	45
PPC, mmHg (2)	PWV (PPC based on **SBP** and **DBP**)	PWV = 0.06 PPC + 0.89; R^2 = 0.719, 14 groups	2, 45
AIx	AP (PPC based on **SBP** and **DBP**)	AIx = 0.68 AP + 18.68; R^2 = 0.397, N = 147	45
AIxC, mmHg	**SBP**	AIxC = 0.67 SBP–32.36; R^2 = 0.769, N = 192	45
$RVSW_{EF}$, ml·mmHg	(PAP and **EDV**) or (**ESV** and MVO_2)	$RVSW_{EF}$ = ΔP·EDV (definition)	38, 43
VAC	**ESV**	VAC = $2.94e^{-0.015 \cdot \text{ESV}}$; R^2 = 0.713, N = 28	36
VACC, ml	**EDV**	VACC = 0.511 EDV + 14.548; R^2 = 0.832, N = 28	36

AP, augmentation pressure; C_1 and C_2, constants derived from the linear ESV versus EDV relationship (39); MAP, mean arterial pressure; Pa, mean aortic pressure during hyperemia; Pd, mean pressure distal to stenosis during hyperemia; PAP, pulmonary arterial pressure; DPVh and DPVr, blood velocity during hyperemia and rest, respectively; DBP, diastolic blood pressure; MVO_2, myocardial oxygen consumption per beat; PP(C), pulse pressure (companion); PWV, pulse wave velocity; $RVSW_{EF}$, right ventricular stroke work (divided by EF); SBP, systolic blood pressure; VAC(C), ventricular-arterial coupling index (companion). The abbreviations written in **bold** refer to the primary physiological variables mentioned in FIGURE 2. *Data referring to daytime measurements only.

sexes, as does the size of the ring finger (D4). Their ratio D2:D4 is an intense field of (pseudo)scientific research, where it only matters to see whether D2/D4 is less than or greater than 1 (41). A similar situation currently applies to a fraction calculated to "physiologically" estimate coronary artery occlusion and then to decide on stenting (44). The precise number is only interpreted as a

Ventricular volume

EDV(i) = end-diastolic volume (index)

ESV(i) = end-systolic volume (index)

Difference SVi = stroke volume index = (EDVi – ESVi) → SVCi = √ {ESVi² + ESVi²}

Ratio EF = ejection fraction = 100 {1 – (ESVi / EDVi)} = 100 {SVi / EDVi} → EFCi = SVCi

Likewise for the various types of strain

Blood pressure

DBP = diastolic blood pressure

SBP = systolic blood pressure

Difference PP = pulse pressure = (SBP – DBP) → PPC = √ {SBP² + DBP²}

Difference AP = augmentation pressure = (SBP – PP) → APC = √ {SBP² + PP²}

Ratio AIx = augmentation index = (AP / Pi) → AIxC = √ {AP² + Pi²}

Coronary flow

Pa = mean aortic pressure during hyperemia

Pd = mean post-stenotic pressure during hyperemia

Difference ΔP = pressure gradient over stenosis = (Pa – Pd) → ΔPC = √ {Pa² + Pd²}

Ratio FFR = fractional flow reserve = Pd / Pa → FFRC = √ {Pa² + Pd²}

Likewise for alternatives such as CFR, iFR, adenosine-free Pd / Pa, etc → CFRC, iFRC

Ventriculo-arterial coupling (VAC)

SV, ESV, Vo (= volume axis intercept of end-systolic elastance)

Ratio VAC = SV / (ESV-Vo) → VACC = √ {SV² + (ESV-Vo)²}

FIGURE 2. **Summary of popular (dimensionless) ratios and differences, including abbreviations, definitions, and formulae used**
The companions (C) are marked in yellow, and the physiologically relevant primary variables are presented in blue. Note that AIx concerns a ratio of two differences, whereas VAC is actually a ratio of two other ratios (i.e., elastances having physical dimensions, which, however, are cancelled out in the ratio). Obviously, SVCi and EFCi share the same hypotenuse. CFR, coronary flow reserve; iFR, instantaneous wave-free ratio; Pi, inflection pressure.

go or no-go decision based on a particular cut-off level (46–48, 66).

Certain ratios are well known from music theory (15) and visual arts (67), contributing to our experience of harmony and beauty when enjoying music, paintings, and masterpieces of architecture. Within this context a remarkable fraction known for millennia refers to the golden number or ratio (with symbol φ), featuring the relationship $\varphi = 1 + (1/\varphi)$. Note that φ is not a rational number but can be approximated by the Fibonacci sequence (23), yielding 1.618.... The golden ratio and the allied golden angle of 137.5° have been found within the proportions and angles seen in nature (notably in phyllotaxis) and also for the human body, including the human heart (22). The reciprocal value

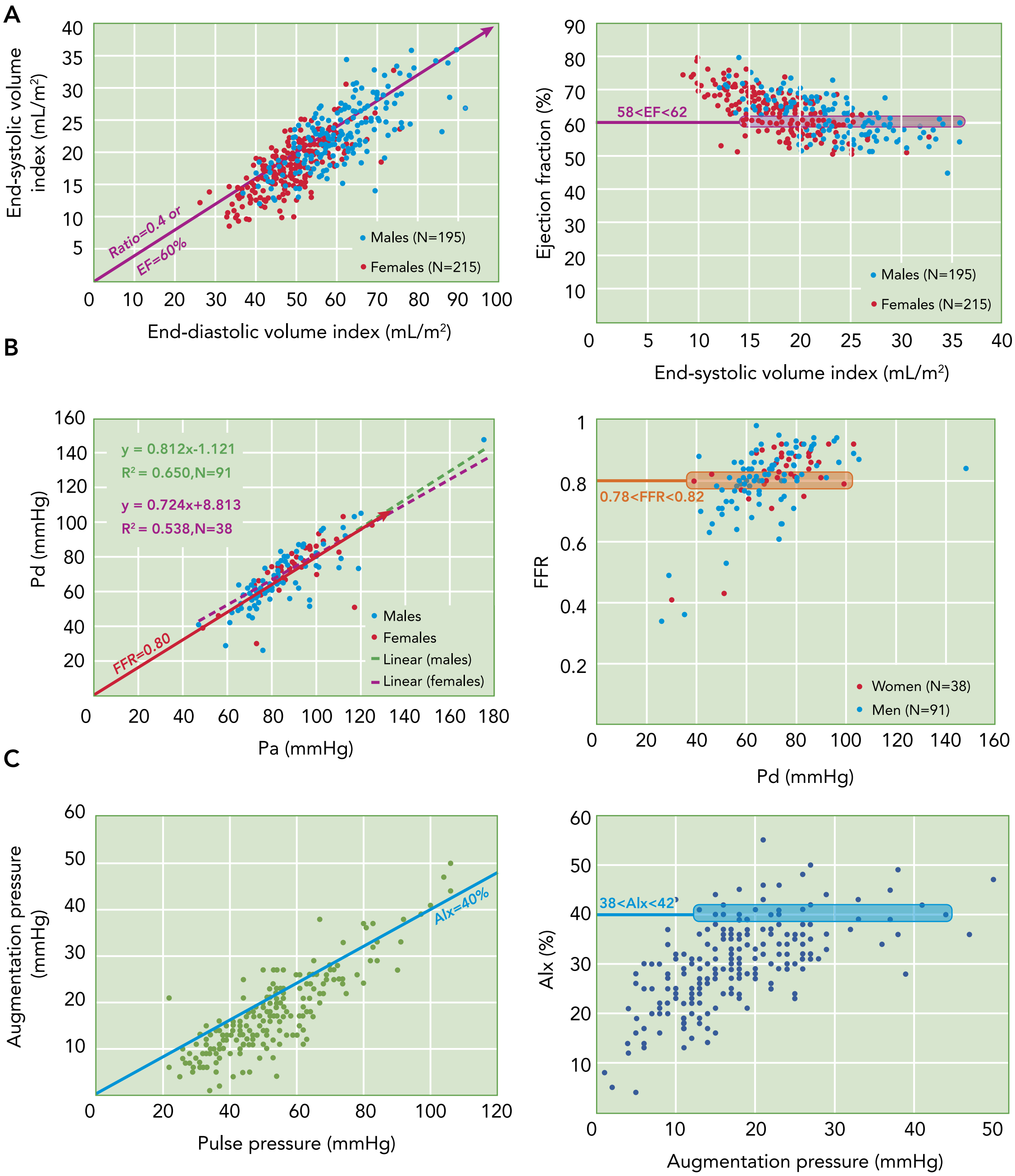

FIGURE 3. **Data pairs in three relevant domains along with associated ratios**
At *left*, primary data pairs are shown, and at *right* the derived ratio is presented as a function of the smaller component shown at *left*. Three major areas are covered. *A*: ventricular volumes resulting in the ratio ejection fraction (EF) based on data referring to healthy adults (37, 38, 42). *B*: aortic and coronary post-stenotic pressure along with fractional flow reserve (FFR) referring to patients (44). *C*: arterial blood pressure characteristics, namely pulse pressure and augmentation pressure, resulting in the ratio called augmentation index (AIx), shown for patients in Ref. 45. The shaded areas (at *right*) indicate a selected region with (almost) constant values for a ratio, corresponding to the slope indicated at *left*. Both presentations illustrate that such a ratio is not unique but is codetermined by another variable to be assigned. Data are from the Department of Cardiovascular Sciences, University of Leuven, Belgium; Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy; and Almazov National Medical Research Centre, Saint-Petersburg, Russian Federation.

of φ ≈ 0.62 comes close to the normal value of ejection fraction (EF). Also, allometric relationships, which apply to all species, show a "normal EF" of 0.64 expressed as a fraction (52). Important here is the insight already gained from characterizing TVs by diagonal size. Although normal humans and animals have at rest nearly the same EF, they can be distinguished on the basis of the diagonal equivalent (coined the *hypotenuse*), which is the companion to EF, as defined in FIGURE 2 and as explained in FIGURE 4.

Finally, we can distinguish hybrid dimensionless variants from other strict dimensionless ratios. The former refer, e.g., to coronary blood flow (CBF; expressed as ml [blood]/ml [tissue]), and in that case they refer to volume of blood in proportion to volume of myocardial tissue mass (8). The latter dimensionless category often refers to paired states in a single subject, such as systole and diastole, or hyperemia versus baseline, and includes metrics such as EF, fractional flow reserve (FFR), etc.

Problems concerning interpretation of a metric or biomarker may arise when some mathematically derived indicators are invoked from the primary variables X and Y, notably differences and ratios. FIGURE 4 shows Y versus X with three superimposed triangles having sides that are multiples, where the next larger triangle has legs X' and Y' and the largest has legs of X″ and Y″. The diagonal is the hypotenuse, and its size is derived from the Pythagorean theorem, yielding 5 units for the smallest triangle. The ratio Y/X equals 0.75 for each triangle shown. Although the ratio is the same, all cases can be distinguished by considering the length of the corresponding hypotenuse. With this observation, we now arrive at the main theme, which we address within the context of ratiology: the hypotenuse may vary while the ratio remains constant (as illustrated in FIGURE 3, LEFT). Interestingly, the hypotenuses estimated from successive elements in the Fibonacci series (1, 2, 3, 5, 8, 13, 21, 34, 55, 89, etc.) approximate again the golden number when their ratio is taken, e.g., $\sqrt{(55^2+89^2)}/\sqrt{(34^2+55^2)} = 1.618031$.

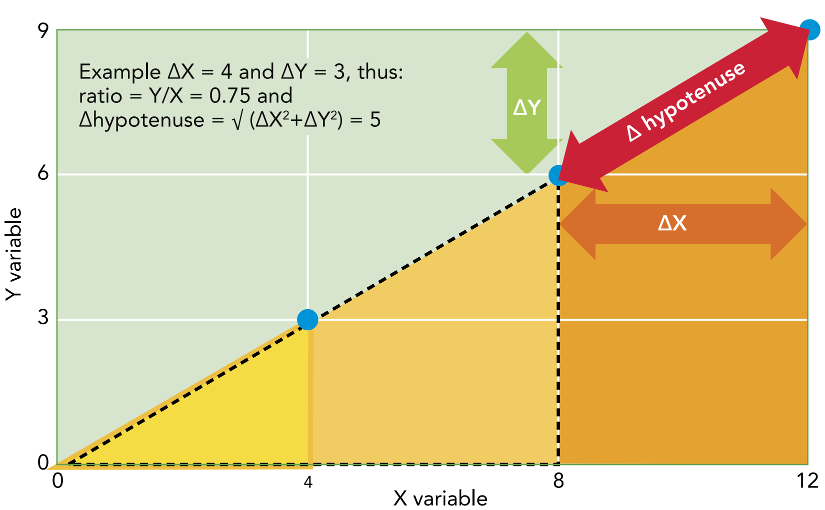

FIGURE 4. **The Pythagorean theorem and hypotenuse**
Three similar triangles (with values of 4, 8, and 12 for the X variable), where the sides show convenient ratios of 3:4:5. This simple example illustrates the case of a constant slope (here 0.75), whereas the hypotenuses (on the diagonal) are multiples of 5 units (as shown above to the right). The coordinates of the blue dots (i.e., upper corners) are determined either by the specific data pair X and Y, or alternatively by the combination of the slope (see ratio) and the length of the hypotenuse. In the text, this concept is applied to the analysis of the ventricular volume domain, coronary flow metrics, and arterial blood pressure.

The Power of the Hypotenuse

To further illustrate the elegance of the hypotenuse concept associated with a ratio, an example will be discussed, based on fundamental properties of pairwise (or coupled) observations. In general, any point in a two-dimensional plane is determined by two coordinates that can be defined using, e.g., a Cartesian or polar coordinate system. A specific example referring to volumes of the left ventricle (LV) is shown in FIGURE 5, illustrating that the dimensionless ratio of two volume determinations does not yield a unique number, as already explained in FIGURE 4. Yet, this particular ratio, being the EF mentioned before, has a rich tradition of over 60 years, exhibiting significant impact with >59,000 publications listed in PubMed (https://www.ncbi.nlm.nih.gov/pubmed/?term=ejection+fraction). It is clear that other components matter. Holt et al. (26) studied LV volume in species ranging from rat to cow and found a nearly linear relationship between ESV and EDV. We have already seen that, in healthy humans, EF can have a rather fixed value, whereas the associated EFC covers a wide range of values (for normal humans in our study from 29 to 97 ml/m^2; see FIGURE 3A). This notion is extended by the data available from the animal study where we calculated 1.6 < EFC < 997 ml. Limitations on the popular EF metric are described in detail elsewhere (37, 38) and can be compensated by also considering other variables such as EDV or the companion of EF. Adding the EFC to the interpretation of these 59,000 papers may enormously affect or even modify the conclusions formulated thus far. In the following paragraphs, the impact of companions referring to additional ratio-based metrics (as summarized in FIGURE 2) will be discussed.

How to Analyze a Fraction and Companion?

To obtain insight into a fraction, it is instructive to create a graphical representation featuring the two components involved along the axes. The information that is lost when constructing the ratio is easily recovered as the companion (37) by the use of the Pythagorean theorem (FIGURE 4). Commonly applied ratios not only include EF but also the various types of strain, ventriculo-arterial coupling (36), FFR, and augmentation index (AIx). Note that all of these ratios are dimensionless, in clear contrast to their corresponding companion (i.e., the hypotenuse). It also should be noted that differences such as PP or stroke volume (SV), and measures obtained by multiplication such as stroke work (43) fall within the category of incomplete metrics. Although differences and metrics obtained by multiplication often carry a sound physical dimension, they do deserve further attention by analyzing the working point or position of the pressure-volume loop in the graph relating the two constituents (43). For any difference, the two primary graphical determinants (FIGURE 5) are the intercept of the iso-line (running parallel to the identity line and therefore always having a slope of 1.0) and the corresponding hypotenuse (45). This combination can always be converted to Cartesian or polar coordinates, as shown in FIGURE 5. Actually, the SVi, ESVi, end-diastolic volume index (EDVi), EF, and their companions SVCi and EFC are interconnected; once two components are known, each of the four other ones can be calculated from the graphical relations shown in FIGURE 5. Interestingly, the companion of SV has the same numerical value as the one for EF (45), as is also evident from FIGURE 5. This notion explains why we see in the figure five types of determinants intersecting at the working point, not six. For the numerical value of the hypotenuse, the preference of variables (in the position of the numerator and the denominator) for the ratio does not matter. However, reversal of the position of the variables may affect statistical comparisons for the ratio (44), as discussed elsewhere (53). This additional complication is not discussed in detail within the present context. Rather we concentrate on the interpretation of the companions under study, with special attention given to possible relevance in terms of sound principles known from physiology. Also, issues around differences will not be discussed at length, since these determinations are often incorporated in composite metrics such as cardiac output (= SV times heart rate) or arterial compliance (= SV/PP) (51).

Although not following our line of reasoning regarding the companion as resulting from the Pythagorean theorem, several investigators discovered that inclusion of a second metric (in addition to a ratio or difference) often helps to further determine risk factors or to better classify certain patient groups. The Framingham heart study found that MAP adds epidemiologically relevant information to the single use of PP (16), whereas others (60) combine EF with end-diastolic pressure to predict long-term outcomes of patients with ST-segment elevation myocardial infarction. These empirically detected additions are important first steps, but such attempts often lack a robust theoretical framework. Reported tentative approaches of these types are likely reflected by the endless stream of publications announcing something novel or better beyond earlier combinations of significant metrics. Thus it is evident that the specific information based on two solid determinations can never be entirely captured in a single metric by applying division, multiplication, or subtraction (FIGURE 1). The need to explore the implications of dimensionless ratios can be met by addressing "ratiology." Absolute figures are better than percentages (9).

As explained in FIGURE 5, every dimensionless ratio as well as certain differences are flanked by an inherent companion, ensuring that precisely two primary data elements are connected to two derived metrics, namely the traditional ratio (or difference) and the companion just retrieved. It must be emphasized that the companions are not "newly introduced" metrics; they exist from the very moment that the fraction was launched as a supposedly useful metric. The companions form an integral part of the ratio-based approach but thus far failed to be generally recognized. This issue being clarified, we need to interpret the "lost son" and search for identification in terms of physiology or analogy with established representations.

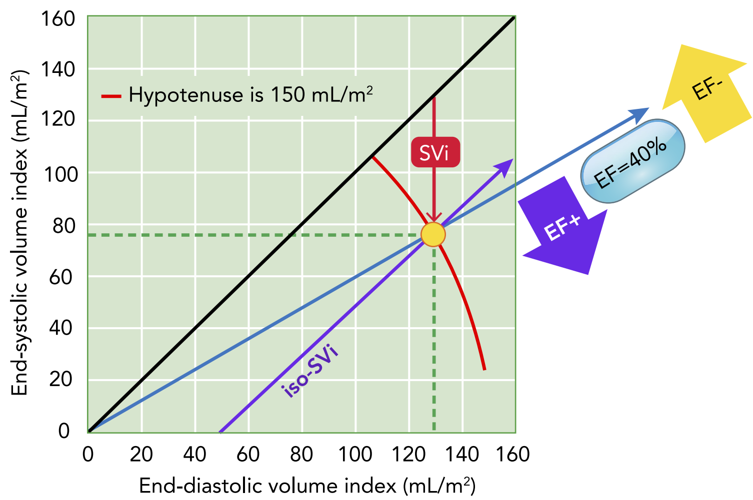

FIGURE 5. **Data pair schematically presented in the two-dimensional space to illustrate limitation of difference and ratio, along with importance of hypotenuse**
Both the traditional Cartesian coordinates (X and Y indicated by the green broken lines), as well as the equivalent polar coordinates (i.e., direction of blue line with arrow head, combined with hypotenuse) are illustrated for a working point (yellow dot) in the volume domain. The polar set includes the slope (i.e., ratio Y/X), corresponding with ejection fraction [$EF = (X - Y)/X$], as well as the hypotenuse (from origin to the yellow dot). The size of the hypotenuse equals $\sqrt{X^2+Y^2}$. The distance (red line with arrow) down from the (black) identity line signifies stroke volume index (SVi). The iso-SVi line (purple) runs parallel to the identity line and represents all states having the same SVi. The actual working point is also found on the intersection of the iso-SVi line and the pertinent iso-hypotenuse curve. All points on the iso-EF line have the same value (here 40%) and can only be individually distinguished by also considering the pertinent length of the hypotenuse.

Interpretation of Fractional Metrics and Their Companions

We state that every ratio- or difference-based metric has a corresponding companion (FIGURES 1 AND 4). The major problem is the fact that the complete class of companion metrics has been neglected thus far. This notion raises the question how various traditional ratios "survived" despite the theoretically derived fundamental limitation. One reason may originate from the fact that a fortunate coincidence promotes a rather trivial connection between two measures, with a single candidate demonstrating relevance for one or more other (independent) reasons. The range for SVi is (during baseline conditions) sufficiently constrained (39) to yield a tight association between EF and ESVi (FIGURE 6). Therefore, it comes not as a total surprise that a ratio such as EF may look meaningful for what turns out to be a secondary reason. In the case of EF, it has been established that ESV presents with demonstrated clinical usefulness (7, 21, 55, 56, 61, 69), besides evidence based on physiology (38). As proposed in the past, EF may derive (FIGURE 6) its clinical utility from the importance of ESV (29, 38). Insight into the companion is facilitated by recognizing that the larger variable of a data pair forms the dominant element in the calculation of the hypotenuse. Turning again to the EF example, we find that EFC is principally determined by end-diastolic volume (EDV), thus indicating that each of the Cartesian constituents plays a dominant role in one polar coordinate (39). It seems that the companion is sometimes "more physiological" than the associated dimensionless ratio (Table 1, and, for example, FIGURES 6 AND 7) because the companion is connected to a variable with clear physiological interpretation and also possesses a sound physical unit.

FIGURE 3, LEFT documents, for the areas under study, the distribution of *X* and *Y* values. Patterns differ, to some extent also being dependent on the specific patient population under study. Importantly, the spread of data points determines characteristics of the associated ratio-based metric and companion. As expected, in FIGURE 3A, we see that data points in the LV volume domain are distributed along a line, because the variation in SVi at rest is rather limited (39). For the pressure domain regarding coronary artery stenoses (FIGURE 3B), the Pd can assume any value below Pa, thus occupying the triangular area below the FFR = 1.0 line. Spread of data points assumes yet another pattern for the aortic pressure-derived metrics (FIGURE 3C), since augmentation pressure varies widely, especially in the lower PP range. Once we have an idea about distributions, the next question is what the ratio Y/X would look like for each of the three situations analyzed (FIGURE 3, RIGHT). This exercise is relevant for our search into the underlying reason why certain ratios apparently exhibit clinical value, despite their overt conceptual shortcoming. If it turns out that a ratio is

FIGURE 6. **Nonlinear inverse relationship between EF and ESVi**
Shown for cardiac patients (90 men, 65 women), along with regression curves determined using EF (%) = $100[1 + (C_1 \cdot \text{ESVi})/(C_2 + \text{ESVi})]$, where C_1 and C_2 are constants (39). Note that the EF range for these patients is larger than for the healthy individuals shown in FIGURE 3A. Data are from Cardiovascular Center, OLV Clinic, Aalst, Belgium.

more exclusively determined by one of its two constituents or a particular combination, then this finding helps the identification process. Our earlier studies on ventricular size already demonstrated that EF [defined as 1–(ESV/EDV)] is more tightly associated with ESV than with EDV in patient studies (39), as well as in a Monte Carlo modeling approach (35). In mathematical terms this means that $1 - (Y/X)$ versus Y is of primary interest, as visualized in FIGURE 3A for healthy individuals and in FIGURE 6 for cardiac patients. Although EF is associated with ESVi, there is no significant connection between EF and EDVi for healthy individuals (37, 38), and the correlation is weak when cardiac patients are considered (29, 34, 39). The nonlinear regression curves for men and women superimpose (FIGURE 6), but average values for ESVi and EF differ (39). The significantly smaller ESVi found in women explains why their EF value is larger and EFC is smaller (37, 40). Clearly, for the strict condition that $Y = (X - \text{constant})$ as, for example, applied to a constant value for SVi (FIGURE 5), an inverse nonlinear relationship results, more or less similar to EF versus ESVi, as observed in patient studies (58). In general, the precise pattern of derived metric values plotted against one variable concerned in the analysis is dictated by stochastic considerations applied to the primary variables involved (57). It remains to be explored to what extent fundamental physiological processes are playing a major role in these mathematically derived patterns. Our proposals for identification of companions are summarized in Table 1. Reference values need to be established for the companions, similar as for the primary metrics (40). Suggestions for cut-off values as in FIGURE 1 require evaluation in future clinical trials, which incorporate the companion.

Metrics Based on a Difference

The procedure required to obtain the companion metric of a difference (a – b) or (b – a) is similar, as outlined for the case of a ratio (FIGURE 5), by considering the red arrow pointing downward from the identity line (black). Instead of volumes (such as SVi, shown in the graphical example), we may also apply this approach to the pressure domain (to derive PP or AP). Differences may subsequently appear in a ratio, as in AIx.

Mathematical Considerations

The pulsatile nature of the pumping action of the heart implies that measurements are often formulated in terms of combined maximum and minimum values of volume and pressure for any given hemodynamic state, such as at rest or during a well-defined level of exercise. In case of blood pressure readings, everyone traditionally adheres to the recording and evaluation of such a data pair, namely systolic blood pressure (SBP) and diastolic pressure (DBP). The combination of SBP and DBP values is employed to define abnormal arterial pressure, although derived metrics such as the difference (PP) are also reported to reflect a risk factor or to assess prognostic information (2). In contrast, no one would routinely consider the ratio of SBP and DBP, although recently the logarithm of such a fraction divided by PP has been introduced to refine calculation of the cardio-ankle vascular index (CAVI) (2). Similarly, the EDV and ESV pair is rarely analyzed in unison, unless presented in the volume regulation graph (31–35, 37–39). Rather, their ratio became widely accepted in clinical practice and is known as EF, being $100 \cdot (1 - \text{ESV/EDV})$ when given as a percentage, and, as shown in FIGURES 3A AND 6, as related to ESVi. Indeed, EF has enjoyed wide interest, e.g., using multivariate analysis, it was found in 1,782 men and women (23–35 yr) without self-reported heart disease that, among other factors, current smoking was positively and independently associated with an ~1% lower EF ($P < 0.01$) (70).

The universal applicability of the ESV versus EDV graph for all four cardiac compartments leads to several immediate consequences. On purely theoretical grounds, it may be expected that EF is inversely related to ESV, based on EF $= [1 + (C_1 \cdot ESV)/(C_2 + ESV)]$, as mentioned before. The derivation is presented elsewhere (32). A further proof based on Monte Carlo simulation (i.e., employing random numbers) has been reported (35). For the left atrium

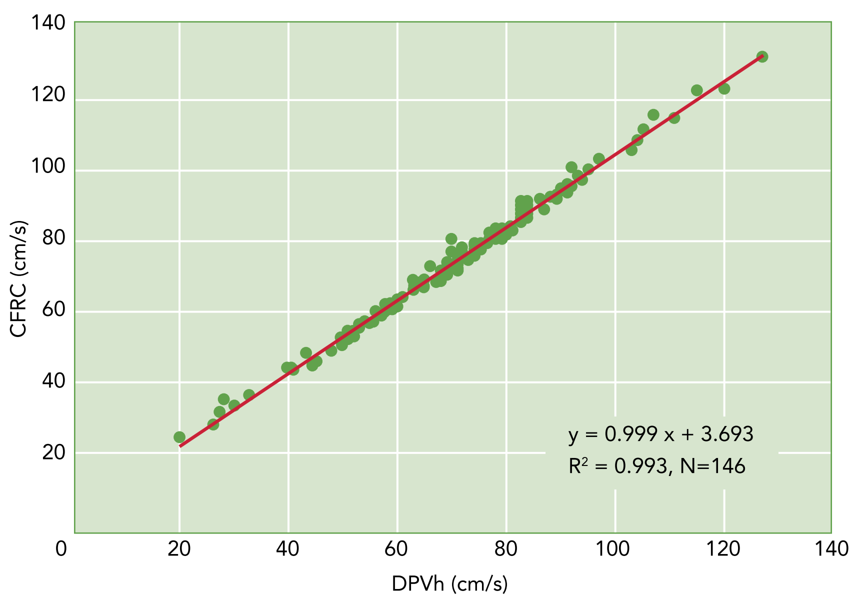

FIGURE 7. **Identification of the companion (C) of coronary fractional reserve (CFR)**
The CFRC shows a high correlation with the hyperemia-induced coronary blood velocity (DPVh). Data are from Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Italy.

(LA), this notion was confirmed in an editorial (14) noticing that LA minimum volume was strongly associated with LA EF in a population (1,142 healthy elderly): LA minimum volume was the strongest correlate of LA EF in every diagnostic subgroup analyzed. Again, this finding is to be expected, since it is essentially based on a mathematical truism (37).

Calibration of Data

In the past, some cardiologists calculated EF without using a grid but rather with the aid of scissors. This procedure means that the contours of systolic and diastolic angiocardiograms were cut out and put on a scale to estimate their weight; then the ratio based on these two readings was employed to estimate EF. In this case, anatomic volumes were reduced to photographic plates in the two-dimensional plane, and relevant portions were converted to weights. Since many metrics are dimensionless ratios, there is indeed no strict need to calibrate the underlying data, as long as they are based on a similar (linear) scale, correctly zeroed, recorded with appropriate drift check, and expressed in identical units. In contrast, carefully calibrated data are required to calculate the companions that do carry familiar units. The fact that the companions are always expressed in terms of common physical units implies a strategic advantage over the mere ratios. Finally, ratios are not necessarily the ultimate measurement goal. In that respect, this survey primarily emphasizes the need and route to analyze both the ratio and the associated companion. Definitively, the two should always be analyzed together. Likewise the two constituent components must be viewed in unison, much like we tend to consider SBP in connection with DBP. As a matter of fact, employing the primary variables may be preferred over the use of derived metrics.

Observations in Various Domains

Cardiac Volume-Related Variables and Derived Metrics

The commonly employed metric EF does not really help to explain how the heart (or ventricle, for that matter) functions. The mere ratio does not provide insight into the workings of the cardiac pump and has no bearing on engineering approaches. In fact, we recently found that rather the "hidden" EFC provides some insight by clearly referring to preload (37). An EF value in the "normal" range may either refer to a healthy individual or to a patient with a particular phenotype (with preserved EF) of severe heart failure (40). Obviously, in the truly symptomatic patient, there are more indicators to differentiate the two options. On the other hand, this particular phenotype of heart failure was not recognized as such until recently (34). Nowadays, prevalence of this category is reported to be larger than the traditional type with reduced EF, especially in women. As an aside, women have higher values for EF, regardless of the presence of heart disease, compared with their matched male counterparts (40). Note also that EF at rest may be depressed with EFC enlarged in a perfectly healthy elite athlete, again indicating that isolated interpretation of EF may be troublesome.

The "mathematical anatomy" of EF has recently been dissected (39). Unfortunately, it is not always appreciated that ESV and EDV yield in population studies a highly linear relationship of the type ESV $= k_1 + k_2 \cdot$EDV, permitting an analytical expression for EF versus ESV, where k_1 and k_2 are regression coefficients (31–35). Anecdotes report that EF has been advanced in 1965 by the (late) psychiatrist Stuart Bartle, but historical facts tell us that the EF concept logically followed from indicator dilution methods, which back in 1951 were employed to determine residual fraction, which equals 1–EF (33). During even earlier studies in 1934, a similar fraction with focus on (patho)physiology was calculated from X-ray imaging (4, 28). In 1959, Gribbe et al. (20) used cineangiocardiographic recordings to relate SV to ESV, a ratio that equals EF/(1–EF). Thus it appears that there is a firm imaging tradition without dominant input from the field of physiology. Actually, physiology textbooks around 1975 (such as those edited by Mountcastle, Selkurt, Ganong, Samson's Wright, and Rushmer) did not even mention EF and were mostly concerned with the Starling mechanism (11, 27) and exploring length-tension relationships. Taken together, there is no evidence that physiologists were the initiators of the EF concept as a metric of "cardiac function." Actually, 3 years after the introduction by Bartle, the idea was challenged on the basis of animal experiments demonstrating load dependence and not being a direct indicator of contractility (49). Over the years, a dozen papers have criticized the EF concept, often by highlighting the (presumed) complexity of the metric, as reviewed elsewhere (33, 34, 37). Investigators involved with animal experimental studies accepted the metric EF, mostly to translate their findings to clinical studies in humans. In addition, the steepness of the (linearized) slope for EF versus ESV (FIGURE 6) was employed to assess survival after recovery from myocardial infarction (69). Although this study is cited more than 2,650 times, no single investigation has ventured to confirm these findings.

The central role of ESV(i) is illustrated in FIGURE 8, which shows that EDV(i), end-systolic elastance (Emax), and the associated volume axis intercept (Vo) are all connected with the core element via relatively simple mathematical expressions (38). The EFC is tied to EDV, as becomes plausible by appreciating that this companion connected to EF is based on ESV and EDV, where the latter is always the greater component. Thus, in the volume domain, the companion to the ratio EF can be identified as being connected to a physiologically relevant variable, namely preload. More advanced approaches to study the pump function employ the pressure-volume loop, where end-systolic elastance (Emax) is defined as ESP/(ESV–Vo), with ESP as end-systolic pressure (38).

Arterial Blood Pressure Metrics

As mentioned, for the interpretation of blood pressure levels, the two original measurements have (very correctly) mostly been analyzed in unison. As common practice, one denotes readings as, e.g., 120 over 80 mmHg. Obviously, this is a meaningful notation, reflecting the full information as originally collected, without simplified derived (and therefore often incomplete) metrics. Interestingly, in cardiac patients, PP is highly correlated with SBP (2). By extension, ratios have rarely been considered in the interpretation of blood pressure data, with the exception of CAVI (2) and the augmentation index (AIx) (45). Interestingly, the former metric is a new ratio based on both a ratio and a difference, namely: ln(SBP/DBP)/PP. This term shows in healthy individuals a mild but significant decrease with aging for the range of 15 through 80 years (2). Even more complex is the metric AIx, consisting of the ratio of two pairs of pressure differences, i.e., augmentation pressure (AP; a difference) divided by the difference formed by PP. Clearly, for arterial blood pressure, the PP needs to be interpreted along with the associated PPC, which appears to be strongly tied to MAP and PWV (45). This notion establishes an interesting novel connection between hemodynamics (i.e., MAP that equals cardiac output times peripheral resistance) and epidemiology relying on PP, as supported by the findings of the Framingham Heart Study (17). Thus PPC may act as a surrogate for MAP and PWV (Table 1).

Coronary System

In their editorial with the subtitle "Are All Things Equal?" mentioned earlier, Kern and Seto (46) discussed various coronary "physiological" measurements and indexes used for ischemic stress testing. The authors noted that, depending on the statistical method, these comparisons seemed to indicate either diagnostic equivalency or high agreement among various approaches. These outcomes may not come as a surprise when we consider the theoretical insight presented in FIGURE 4. All ratios resulting from values of Y over X are likely to generate somewhat similar values as long as the distributions of data are comparable. The latter constraint is easily met when the same patients are (nearly) simultaneously studied using slightly different methods. In a meta-analysis (14 studies comprising 7,004 lesions) comparing FFR with an adenosine-free alternative, excellent agreement was found, although cut-off levels for the more attractive adenosine-free candidate ranged from 0.90 to 0.97 (54). Sex-specific differences regarding the coronary circulation and relevant pathophysiology are extensively described (65). However, thus far, differences have just been investigated at the "ratio level," with only recent attention given to the companions FFRC and CFRC (44). Focus has been on occlusion of major epicardial vessels, where FFR is employed. However, coronary microvascular dysfunction may also be significant and requires adequate study (1), particularly in women, e.g., by CFR. Both FFR and CFR studies will next be addressed. Simplified models of the coronary circulation are often used in deriving such indexes, encountering criticism (24, 64). As mentioned, some simple considerations concerning distributions of data pairs can be formulated (FIGURE 3). The numerical value of a ratio (Pd/Pa) strongly depends on the difference (Pa–Pd). For LV volume, this difference (SVi) is rather fixed (at rest, and only slightly modulated by heart rate). The same holds for PP, in the case of arterial pressure. The situation for the coronary system is different, where Pa can vary within limits (say 80–160 mmHg, i.e., a twofold range), whereas Pd can be anything $<$ Pa. The same line of reasoning applies to CFR. Therefore, these ratios potentially show a weaker correlation with the smaller constituent being Pd and

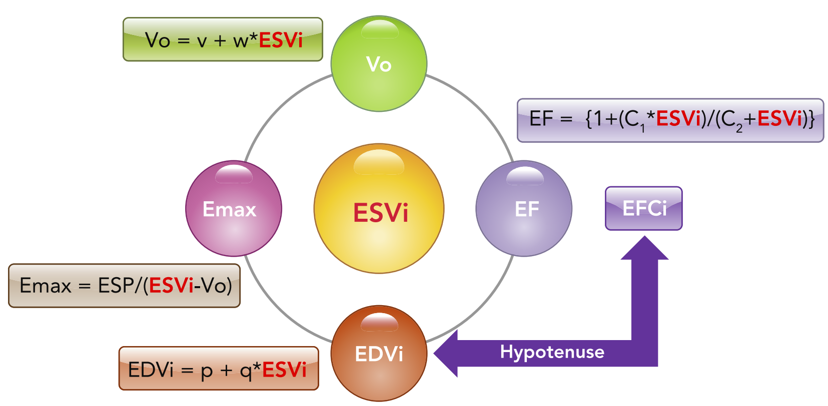

FIGURE 8. **A central role in cardiac dynamics is played by the end-systolic volume index**
This pivotal variable relates to the end-diastolic volume index (EDVi), yielding the fundamental volume regulation graph (31). The ESVi is also associated with ejection fraction (EF), as well as with the two components of the end-systolic pressure-volume relationship, i.e., end-systolic elastance (Emax) and the volume axis intercept (Vo). All mathematical connections and statistical associations are presented in the main text, with the exception of Vo = v + w·ESVi (40). EFC is the companion to EF and is linearly related to EDVi (37). The scheme refers to the left ventricle, and mutatis mutandis also applies to the right ventricle. Volumes are indexed (i) for body surface area. ESP, end-systolic pressure.

DPVr, respectively (44). Rather, they correlate with the pressure gradient (in case of FFR) and the recruitable (increment) flow (for CFR).

Fractional Flow Reserve. The FFR metric originated around 1991 from cardiology centers (Nijmegen, later Eindhoven, both in The Netherlands; Aalst in Belgium; and Houston, TX), but was challenged by physiologists, notably by the Spaan (64) group (from Leiden, later in Amsterdam). Myocardial resistance is assumed to be independent of factors such as driving pressure and cardiac muscle contraction (68), but these simplifications are not always justified. Furthermore, there is a difference between pressure-derived (shown in FIGURE 1, BOTTOM LEFT) and flow-derived FFR. It was concluded that clinical studies of coronary physiology would benefit greatly from combined measurements of coronary flow or velocity and pressure (64). Very unfortunately, this type of fundamental research is largely overthrown by the tsunami of papers on ever simplifying approximations, mostly based on ratios. Some of those newer methods, including the instantaneous wave-free approach, are discussed in a recent editorial (47). The outcomes of our studies on FFR and FFRC are summarized in Table 1.

Coronary Flow Reserve. CFR is a dimensionless ratio created by dividing blood velocity data (shown in FIGURE 1, BOTTOM RIGHT) obtained during hyperemia by those measured during baseline (19). The first report on CFR resulted from animal studies that formed the physiological basis for assessing a critical coronary stenosis (18). The approach has been challenged on the grounds of three factors that need consideration when assessing CFR: *1*) maximal flow achieved by increasing doses of a vasodilator or by examining peak reactive hyperemia may be flawed; *2*) changes in total reserve might not reflect changes in subendocardial flow reserve; *3*) marked heterogeneity of flow reserve exists, and therefore total flow reserve does not indicate when small regions are becoming ischemic (24). Anyway, a balanced discussion awaits consideration of the companion CFRC (44). Our findings on CFR and CFRC are presented in Table 1.

The Physiology Content of a Ratio

One may wonder whether a dimensionless ratio has scientific meaning to the same degree as the information carried by its constituents. Also, it is questionable whether such ratios are truly rooted in basic concepts founded on physiology. To address this issue, a comparison between arterial blood pressure and ventricular volume is fascinating and instructive for a number of reasons. In both systems, maximum and minimum values are considered important, and the difference is judged relevant, being PP and SV, respectively. For the heart, the single value reflected by the ratio EF became a popular measure, whereas for the arterial system the tradition of evaluating SBP and DBP remained without dispute. If we would learn that the ratio of DBP to SBP is, for example, 0.55, then we really do not know whether this is an emergency case. Likewise, the utility of the single measure of PP is probably exaggerated, and in fact is already supplemented by MAP. The potential clinical value of the widening of PP as a cardiovascular disease (CVD) risk factor was first suggested in a seminal publication in 1989 (13). Since then, the Framingham Heart Study investigators and others, using the combination of MAP and PP rather than any single BP component separately (SBP, DBP, MAP, or PP), improved the fit for predicting CVD collectively, or coronary heart disease, heart failure, and stroke separately (17).

Let us return to the earlier question concerning the best intracoronary ischemic parameter: "Are all things equal?" (46). With the preceding considerations in mind, our answer is: "Yes, all seem nearly equal. Often for stochastically obvious reasons (57), not necessarily because of (underlying) physiology." The two components of a dimensionless ratio are often coupled, rarely random (FIGURE 3). As a matter of fact, over recent years, a number of additional resting indexes [i.e., resting full-cycle ratio (RFR), resting pressure ratio during the complete duration of diastole (dPR), resting pressure ratio during 25–75% of diastole (dPR25–75), resting pressure ratio at midpoint of diastole (dPRmid), etc.] have been described and appear to compare well with the diagnostic performance of either FFR or iFR (66). It seems that ratios such as RFR, dPR, and variants refer to signal processing techniques rather than to fundamentals known from physiology. At best, their companions may have a connection with variables derived from physiology.

Physiology and Beyond

As the physiological importance of the blood-pressure is more recognised, and more observation and research is undertaken in connexion with it, I expect that, instead of pages, it will require volumes to do it justice.
G. Hoggan *(25).*

Although the importance of (measuring and correcting abnormal values regarding) blood pressure cannot be overestimated, it must be conceded that the scope of physiology has been extended to what seem somewhat remote areas, including marriage (3). Limiting the discussion to ratios commonly used in cardiology, we are faced with a delicate question concerning the physiological basis. The combination of anatomy and physiology usually refers to "structure and function." In the case of evaluation of the heart, the function component is often captured by EF. The discipline of physiology is a field within the basic sciences that employs exploratory methods to characterize functional aspects of living systems (50). Investigations rely on systematic measurements using appropriate tools, explorations of the consequences of selective disturbances, and modeling work, both in experimental animals and in in silico studies. Outcomes of these studies can often be translated into important information. Although certain observations derived from the clinic can be extremely helpful to guide or prioritize research in selected areas of physiology, it is imperative to adhere to a unidirectional pathway of established methods. Admittedly, techniques that are feasible in the laboratory are not always manageable in the clinical situation, and certain compromises are therefore often acceptable. On the other hand, it is important to guard that convenient approximations, which over the years became routine in patient care and management, are too quickly adopted as a "practical gold standard" in the physiology laboratory without careful evaluation of merits and possible limitations using principles known from physiology.

Conclusions and Opportunities

Any dimensionless ratio-based metric is considered incomplete, as long as it has not been demonstrated that the companion carries no clinically relevant utility. Thus, welcome to the complementary family of metrics! The existence of companions also emphasizes the need to study in unison the two constituent components of any ratio. The companion type of metric may be a more powerful descriptor of sex-specific characteristics because intrinsic age- or size-related differences are "amplified" in the hypotenuse, which considers the sum of squares (FIGURE 4), whereas such differences have the risk of largely being cancelled out in plain ratios (FIGURE 5). It seems that the companion is sometimes "more physiological" than the associated dimensionless ratio, notably for EF, because the EFC is connected to a clear physiological interpretation (namely preload). Although issues around differences received less attention, it is evident that their companions may also reveal relevant aspects. For example, PPC is associated with PWV (Table 1), which suggests the attractive option to derive arterial stiffness from peripheral pressure data at a single site (e.g., brachial).

Remarkably, some ratios discussed here have never been launched by physiologists. Often it is difficult to trace the origin, while current reports are sometimes confusing, as described elsewhere (33, 34, 37). Apparently, ratios creep in (FIGURE 1) and are easily taken for granted, promoted by their ease of use, including the practical convenience of accepting uncalibrated data. Anecdotes on the history of EF can be found elsewhere (33, 34, 37).

Presentation of complex data in graphs with high dimensionality can be applied to provide better insight. FIGURE 5 documents ESVi, EDVi, SVi, SViC, EF, and EFC already in a 2D diagram for one individual at a specific point in time. Multiple working points can be added to map a trajectory, reflecting prevailing details when circumstances change as a disease process progresses or after intervention takes place. The question has been raised of whether dimensionality is a curse or a blessing to personalized medicine, while referring to the complexity of childhood leukemias (10). The authors argued that recent technologies for sense-making permit the holistic interrogation of complex and voluminous data, often using visual analytic tools that display the data in feature space and producing dynamic graphical representations that capture all the biological dimensions for an individual, showing how a patient is unique within the cohort. The rapid progress of bioimaging methods offers specific tools and opportunities, and should be grasped eagerly by physiologists (59). Hence, also in cardiophysiology, this approach needs to be exploited to gain maximum insight into complex patient data available, rather than staring at ratios. Coordinated action by a multidisciplinary team (including physiologists) should likely be required to perform such a task, exceeding the mere analysis of dimensionless ratios. As emphasized before, physiology can transform medicine (62). Particularly, thus far, the field of cardiology did not exploit the full capabilities and may therefore strongly benefit from such advancements (12). In the past, it has been voiced that physiology is an "old science" that can be dropped to stay "current" (5). Despite such worries, it was pointed out that physiology is a vital discipline (50), and the field is flourishing (63). The present contribution illustrates that, in a certain sense, the area of cardiac physiology may be even more vibrant than thought, if its exponents are indeed ready to take the lead in developing new (and better) methods to analyze the cardiovascular system.

It is important to acknowledge that the new class of companions is not a recent invention. Actually, the companions existed from the very first moment that the ratios and differences were introduced. Although a ratio or difference in itself has limited meaning, the corresponding companion has sound relevance and can often be identified as a physiologically relevant characteristic. Companions have interesting advantages: they are expressed in physical units, are invariant for the definition of the ratio (in terms of preferred position for numerator and denominator), can often be associated with hemodynamic variables or findings known from epidemiology, and may more clearly highlight sex-specific differences.

Finally, we maintain that interpretation of the primary data is more obvious than consideration of ratios, which tend to offer a misleading attractiveness. The alleged convenience of a subset of ratios is barely supported by the necessity of considering their elaborative companions. Nonetheless, Cartesian and polar coordinates are fully equivalent. ■

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P.L.K. conceived and designed research; P.L.K., R.A.P., and N.H. analyzed data; P.L.K. prepared figures; P.L.K. drafted manuscript; P.L.K., R.A.P., and N.H. edited and revised manuscript; P.L.K., R.A.P., and N.H. approved final version of manuscript; R.A.P. and N.H. interpreted results of experiments.

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