# Cardiac Risk Assessment: When and Who?

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*And Adam lived a hundred and thirty years, and begat a son and called him Seth. And the days of Adam after he had begotten Seth were eight hundred years, and he begat sons and daughters. And all the days that Adam lived were nine hundred and thirty years, and he died.*

—Genesis 5:3–5

Think about the above lines taken from the *Old Testament:* At 130 years of age, Adam begat a son and at 800 he kept going, quitting this earthly life at 930. These numbers surpass by far the limits our current experience teaches us, however, perhaps a life span into the hundreds of years is … What if, in the future, science were to do away with disease? What then would cause people to die: accidents, killings, wars? How old would old age be? Aging has always been a hot topic for research (with considerable quackery, too). For example, animals with a slow metabolism tend to live longer than those with a fast metabolism. Compare the average life span of a mouse with that of a turtle. Apparently, meditators are able to slow their metabolism down [1].

Doubtless, indeed, is the interest man has had since the beginning of life to know how much longer he would be able to enjoy the beauty of the world, at least those of us who are able to enjoy it. Many efforts have been made in this direction, e.g., the philosopher's stone. There are scientists who sustain that human immortality will be achievable in the first decades of the current century. The fact is that physicians, from the beginning of their career, try to predict a disease or the possible outcome of any illness, either in the short or long run. The term *prognosis* refers to a physician's statement or claim that a particular health event will occur in the future. The *Merriam-Webster Collegiate Dictionary* defines prognostication as auguring, forecasting, or foretelling.

Medical practices improved significantly during the 17th and 18th centuries, when scientific societies showed up in several European cities and when journals became a medium to share knowledge. Hospitals also experienced dramatic advances [2]. For example, Anton van Leeuwenhoek (1632–1723) discovered red blood cells, bacteria, and protozoa using a simple microscope, and Edward Jenner (1749–1823) found a link between cowpox and smallpox and came up with the first vaccine. Imagine the impact that these discoveries had; however, old, dangerous therapeutic practices, such as bleeding or uncontrolled electric shocks, continued with a rather light attitude. In fact, these procedures were used to treat acute hypertensive spells and, in some cases, human behavioral disorders well into the 20th century.

A more solid scientific basis for medical practice was developed during the second half of the 19th century and throughout the 20th century, with outstanding findings being made, along with direct contributions from the physical sciences and the improvement of sanitation measures (yes, simple as it may sound, water systems, sewers, streets, and personal hygiene customs). Specialization has become mandatory, requiring advanced knowledge, and hence it is impossible for any physician to become an expert in every field.

Empiricism dominated medicine for a long time, claiming that experience was the only source of all knowledge; consequently, the medical practice was for a very long time almost exclusively based on experience (leaving aside charlatanism and witch doctors). Only data in the form of clinical observations could produce reliable information. This concept can be traced back to Hippocrates (~460–370 B.C.). The older the physician, the stronger and more reliable his assessments. From this idea comes the frequently mentioned comment regarding the "good clinical eye" a particular doctor has. Such experience is still considered to be valuable, and it should certainly be respected and not looked down on; however, it may fail, and other methods can take over at least partially for the medical evaluation and prognosis.

The truth is that, even though sparse successful and clever attempts were made, no serious medical prediction of any kind could be put forward before the year 1900; see the excellent and comprehensive references [3] and [4]. Well into the 20th century, medical predictions began to gain some credibility, but within rather large error margins. In fact, rather than prediction, we should speak more in terms of health risk, expressed as a probability value. Cardiology is perhaps the most advanced area in this respect; this article will restrict itself to answering the questions of when and who began the evaluation of cardiac risk.

## From Statistical Data

The systematic collection of medical data (counting cases of diseases and deaths and recording their geographical distribution) constitutes a starting line to quantifying medicine, i.e., putting numbers in a seemingly numberless world. It began around 1749, although there have been changes in the meaning of the word *statistics*. Statistics originally referred only to "states," i.e., (according to *Merriam-Webster's Collegiate Dictionary*), "mode or condition of being" (state of readiness), "condition of mind"

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(a nervous state), "condition of tension or excitement," "condition in the physical being of something" (larval state, gaseous state), or "any condition characterized by a quantity" (energy, electric potential); it may even describe a social position. All these definitions refer to static conditions as opposed to dynamic situations.

Today, the definition of the word statistics includes the numerical analysis and interpretation of such states. Statistical activities are often associated with models and probabilities. Interestingly enough, in the writings of Claudius Galenus (129–c. 200/216 A.D.), known as Galen of Pergamon, the word *probability* is used many times, but with no mathematical framework. The *Talmud* (text of Rabbinic Judaism, 300–500 A.D.) alludes to the probability of two events. In the recent past, Girolamo Cardano (1501–1576) formulated elementary rules of probability, and Galileo Galilei (1564–1642) expanded them by calculating probabilities when throwing two dice. Other prominent scientists contributed and refined the theory of statistics. This knowledge paved the way for modern statistics, which essentially began with the use of actuarial tables to determine insurance for merchant ships. John Graunt (1620–1674) categorized the cause of death of the London population using statistical sampling. He postulated:

> If any man lived ten years longer, it is the same that one of any ten might die within one year, so to better understand the hazard they are in.

Graunt's early and rough statistics can be compared to data from the United States in 1993 (Figure 1). In the statistical sense, life expectancy (different from life span) is the probable number of years of life remaining at a given age according to a particular mortality experience. Life expectancy is based on the analysis of life or actuarial tables. With the augmentation in statistical thinking, Jacob Bernoulli (1654–1705) came up with the law of large numbers, which states that, as the number of observations increases, the actual frequency of an event would approach its theoretical probability. This law is the basis for all modern statistical inferences. Incidentally, the Bernouilli family produced many prominent scientists.

Despite great advances in knowledge during the first part of the 20th century, physicians were not using statistics; in fact, there was often sheer visceral rejection of them. The case study was preferred to "prove" that a treatment was beneficial or that an etiology was the cause of an illness. There were intense battles between those relatively few physicians who wanted to use statistical sampling and those (a majority of physicians) who believed in the power of inductive reasoning from physiological experiments. Pierre Simon Laplace (1749–1827) introduced the idea that any knowledge is intrinsically uncertain and, therefore, probabilistic in nature. Medicine, instead, was based on deductions from experience and induction from physiology, which were felt to be more important than the "calculus of probability."

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Nonetheless, people kept thinking and working. Francis Galton (1822–1911), the cousin of Charles Darwin (the biologist, 1809–1882), was a statistician. He is recognized as the creator of regression analysis in 1877 and the concept of correlation in 1888, while Karl Pearson (1857–1936) is often considered to be the founder of biostatistics. He is an antecessor of Ronald Aylmer Fisher (1890–1962), who created the concept of analysis of variance, which is now commonly used in many calculations.

The concepts and techniques introduced by these pioneering researchers permitted the organization and completion of the first clinical trial in 1946, which was sponsored by the British Medical Research Council to test whether streptomycin was effective in tuberculosis treatment. Many clinical trials were carried out thereafter, even though there was significant resistance in spite of their effectiveness in practice.

Probability of Survival

| Age | 1660 | 1993 |
|---|---|---|
| 0 | 100% | 100% |
| 26 | 25% | 98% |
| 46 | 10% | 95% |
| 76 | 1% | 70% |

**FIGURE 1** First actuarial table. The first row states that at birth, a person either in 1660 or in 1993, had 100% probability of survival. However, as time proceeded, his or her survival chances dropped much more heavily in 1660 than in 1993.

The most impressive and dramatic saga is of the two large-scale tests for polio vaccines by Jonas E. Salk (1914–1995) and his eternal rival Albert B. Sabin (1906–1993) [5].

## Evidence-Based Medicine

Evidence-based medicine (EBM) is defined as the process of systematically reviewing, appraising, and using clinical research findings to aid the delivery of optimum clinical care to patients [6]. Although the concept is adopted from clinical trials and their statistical processing and interpretation [7], it can be thought of as a much more elaborate philosophical position based on the old system that valued experience gained in medical practice above all else. Previously, large variations were found in the amount of care delivered to similar populations, leading to questions regarding the interpretation of diagnostic tests, the harm associated with exposure to an agent, the prognosis of disease, the effectiveness of a therapeutic intervention, and the costs and consequences of clinical decisions. EBM was a paradigm shift, representing a breakdown of traditional ideas and the acceptance of the scientific method as the driving force in medical advancement.

Simply stated, EBM is the application of the best evidence that can be found in the medical literature to a patient with a specific medical problem [8]. Statistics and clinical trials are its essential components, but empiricism, which remains in the background, cannot be left out, although it is somewhat hidden. The discussion thus far is applicable to medical care at large and, obviously, to cardiac risk evaluation.

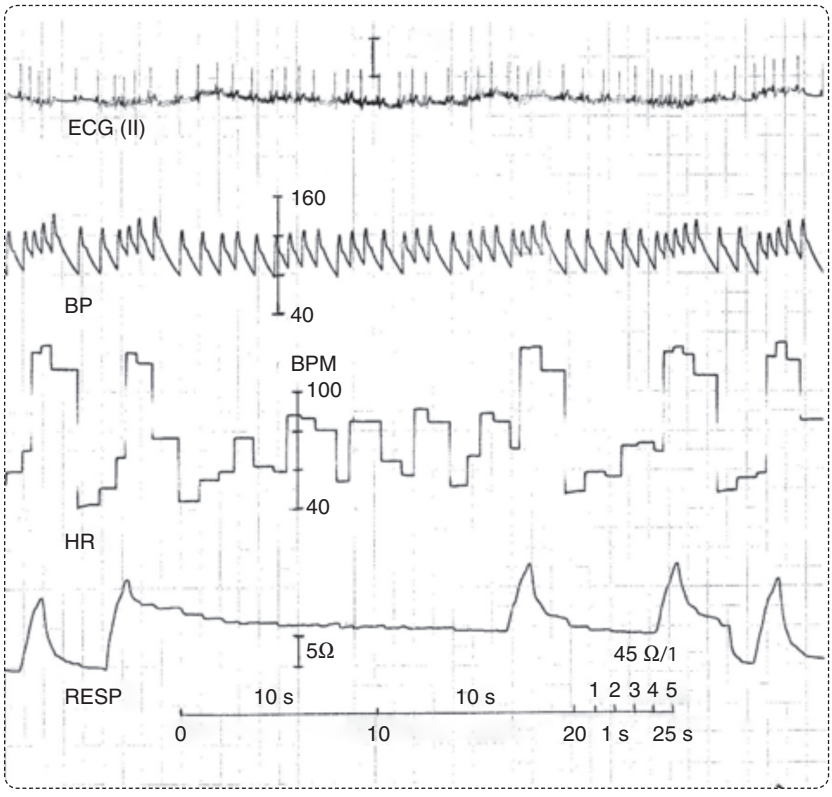


**FIGURE 2** RHRR is shown in an anesthetized dog. Upper channel: ECG (lead II); second channel: blood pressure recorded by direct cannulation of one carotid artery and an external transducer (Statham, now long obsolete); third channel: HR recorded with a tachometer in beats per minute; lower channel: respiratory thoracic movements detected by the impedance technique. Air volume produced a change of about 45 Ω/L, meaning a tidal volume in the order of 200 $cm^3$, perhaps too large for a 16-kg (or 35-lb) dog. It should be stated that this calibration was rather rough, done with a big syringe injecting known volumes of air. The long horizontal bar shows time marks in seconds. Observe the clear increase in HR during inspiration. There was a period of apnea of about 20 s, but cardiac frequency kept its oscillations, although less marked. These records were obtained by author Max E. Valentinuzzi, using a now obsolete ink and pen four-channel physiograph, when with the Department of Physiology at Baylor College of Medicine back in the 1960s. Hence, these records are already historic (50 years old).

## Through Mathematical Models

Let us now get into mathematical models and their role in cardiac risk assessment, which is our main concern here. Mathematical models were primarily used in the second half of the 20th century, although a few antecedents can be found in earlier contributions [9]. Since this is not a review, we will try to concentrate on its relatively recent historical roots.

### *Heart Rate Variability*

To place this predictor in the group of mathematical models is more arbitrary than real because the mathematics came much later, well after the basic physiological phenomenon was described and named, known as either sinus arrhythmia (SA) or respiratory heart rate response or reflex (RHRR). The concept of RHRR is a mixture of physiological knowledge developed gradually over a long period of time and an explosion of discrete mathematical thinking standing on the almost almighty computer. Each person shows cyclical changes in his or her cardiac frequencies, which are more noticeable in infants than adults. Place your ear over the chest of a one-year-old child when sleeping quietly and notice how his or her heart rate (HR) increases during inspiration and significantly decreases during expiration. You might get scared, thinking that the heart has stopped working. Sheep, as well as several aquatic species (such as dolphins), display a good RHRR. Experimentally, it has been observed in dogs (Figure 2) and can be enhanced by using adequate anesthetic agents that potentiate vagal activity (such as morphine).

RHRR is a normal phenomenon, and an alarm should be raised if it disappears, as this might lead to serious trouble. One of the authors of this article, Max E. Valentinuzzi, remembers well a lecture given about 50 years ago by Dr. Carlos Vallbona at Baylor College of Medicine in the 1960s. Dr. Vallbona showed a record (a film) of a patient who displayed a constant HR, which resulted in his demise. He firmly stated, "This pathophysiological fact means irreversible central nervous system damage with 100% death prognosis in the following days." Not long ago, George E. Billman updated the historical development of this interesting and still puzzling phenomenon [10]. Somewhat paraphrasing from the latter author, he said, "HR variation (HRV) and SA are not quite the same; however, these terms are often mixed as equivalent. They reflect changes in cardiac autonomic regulation, but the contributions of both divisions (para- and sympathetic) of the autonomic nervous system (ANS) still remain a subject of investigation,"

In the first part of the previous century, Gleb Vasilevich Anrep (1889–1955), a Russian physiologist, and his coworkers described the respiratory variations of the HR [11]. Citing several previous works by E. Hering from as early as 1871, [12], they began conducting a study at the Physiological Laboratory of Cambridge, United Kingdom, in 1929, and continued it in Cairo, Egypt. Their experiments indicated that there were reflex and central components; however, interactions between the two components produced unreliable results. The paper is fully physiological in nature and is based on experimental observations.

Ewald Hering (1834–1918) was a professor of physiology at the University of Prague, Czechoslovakia, for 25 years before succeeding Carl Ludwig (who died in 1895), at the University of Leipzig, Germany [13]–[15]. Hering, known as codiscoverer of the Hering–Breuer reflex, proposed a theory for the regulation of respiration. He is often confused with his son (Hering, the younger, of Prague and Cologne, carrying the same first name), who was also a physiologist and contributed to the understanding of the carotid

sinus reflex. After 1936, there is a gap in the RHRR literature until the 1960s and 1970s, when several papers were published. Perhaps the years before and during World War II (1939–1945) and its aftermath forced a temporary and rather prolonged recess of the subject [16]–[22], accounting for the paucity of publications on the subject for about 25 years (between 1936 and 1960, to the best of our knowledge).

The 1970s brought another series of contributions [23]–[26]. Womack, in 1971, applied spectral analysis, apparently for the first time, to RHRR. Nonetheless, Anrep's paper stands out as pioneering and highly relevant. Another paper that provides considerable information was produced by a task force of the European Society of Cardiology [27]. The authors point out that, between 1975 and 1995, a significant relationship between the ANS and cardiovascular mortality was observed, including sudden cardiac death. Such awareness led to further development of quantitative markers of autonomic activity, with HRV being one of the most promising ones. However, the significance and meaning of different measures of HRV are rather complex. Such a situation led the European Society of Cardiology and the North American Society of Pacing and Electrophysiology to constitute another task force for the development of adequate standards, such as defining of terms, specifying methods of measurement, and defining physiological and pathophysiological correlates. Members of the task force belong to the fields of mathematics, engineering, physiology, and clinical medicine. Thus, it clearly recognizes the interdisciplinary nature of the problem. The number of references on HR variability is so large that it is not possible to review them all [28].

The current situation states that risk stratification in patients with heart failure and myocardial infarction can be carried out through HRV; when such variability is low, it becomes a strong predictor of mortality. Determination of reliable quantification and error margins is still needed. However, there are voices that challenge the latter contention; the simplest would ask how low is *low*. It represents a nice research avenue for the future generation.

### *Allometric Model: An Old Concept Revisited in Cardiology*

The concept of allometry was developed in 1891 by a German physician named Otto Snell, who wanted to compare the mental capabilities of different mammals in terms of their brain size [29]. Since he was aware that the brain makes up a smaller fraction of the total body mass in larger mammals, he developed an equation to express the mass of the brain in relation to the body mass. The equation follows the power-law form, i.e., $Y = cM^b$, where $Y$ is brain size and $M$ is body mass, with the coefficients $c$ and $b$ determined empirically.

Sir D'Arcy Wentworth Thompson (1860–1948), a Scottish biologist and mathematician, is mainly remembered as the author of the book *On Growth and Form* [30], which was written largely at the University of Dundee in 1915 but published two years later due to wartime shortages. In this study, he went against the biologists of the time, who claimed that evolution determined the form and structure of living organisms, underestimating the roles of physical laws. He proposed that structuralism, instead of survival of the fittest, determines the form of species (accepting that structuralism views phenomena that are intelligible only through their interrelations within a bigger system—a structure, as a kind of would-be scaffold). In 1932, Julian Sorell Huxley (1887–1975), an English evolutionary biologist, first coined the term *allometry* (from the Greek word *allo*, meaning *other*), i.e., the measurement of other parts, to describe the relationship between any characteristic and body mass [31]. His achievements were wide and varied, and sometimes even controversial.

Allometry was mainly used to standardize and make data applicable across different species. Stan L. Lindstedt, an investigator interested in size constraints who is now a professor at the University of Arizona, and other collaborators [32] extended the use of the term allometry from organ size to functions and cycles. In fact, one of his older papers [33] is still well cited. He defined biological times (such as HR) as body-mass-dependent variables and also found that the resultant exponents $b$ are often grouped according to categories of variables providing insights into body-size "principles of design" that would dictate several aspects of function across mammalian species. Several examples: volumes or capacities of the body scale linearly with body mass ($b = 1$); body mass exponents describing the lengths of biological times (HR, for instance) are nearly a quarter ($b = 1/4$); volume-rate parameters, say, metabolic rate or cardiac output can be obtained as $M^{3/4}$ [34]. Lindstedt and his collaborators gathered information from older studies and compiled data that was enough to make quite a complete list of normal physiological and anatomical values for four species: rats, mice, dogs, and humans [35]. After compilation, the pattern followed by the body-mass exponents confirmed the above categories and limited the use of allometry to a mere description of patterns. In his 1986 paper [35], Lindstedt cautiously stated: "Allometric equations describe patterns, but they are not precise predictive laws. Additional data could modify the above equations."

Noujaim et al. [36], at the Institute for Cardiovascular Research and Department of Pharmacology, Upstate Medical University, Syracuse, New York, applied the concept of allometry to a purely electrocardiological parameter such as the time taken by an electrical impulse generated in the sinoatrial node to propagate from atria to ventricles: the PR interval. In their work, the authors confirmed the body-mass exponent of $\mathbf{M}^{1/4}$. This contribution put for the first time an electrocardiographic parameter under the allometric light. Following this line, Bonomini et al. [37], at the University of Buenos Aires, Argentina, recently investigated the allometric nature of the electrocardiographic ST-deviation to predict cardiac risk using reported clinical data.

In conclusion, the allometric model is not only useful in describing patterns but also poses itself as a tool to devise electrocardiographic indexes or predict cardiac risk with very few simple resources, becoming an appealing approach to a wide range of pathologies in cardiology. Let us close this section with Lindstedt and Calder's own deep thoughts [33]:

> If there is a lesson to be drawn from comparative gerontology, it is not a suggestion of how to

> increase life span, which is itself a second- or third-stage consequence of metabolic logistics. Life ends when these vital functions fail. The goal of gerontology should not be to prolong life in quantity of years, but to prolong the living of a full life of unimpaired function during the allotted $\mathbf{M}^{1/4}$ span of years. [33]

This paragraph might conflict with other standings based on different philosophical positions.

### *Vectorcardiography as Cardiac Risk Predictor (or Cardiac Monitor)*

As early as 1920, Hubert Mann, at Mount Sinai Hospital, manually drew the successive instant vectors using the standard electrocardiography (ECG) leads, as described by Einthoven et al. [38], [39] in 1913. Mann called it the *monocardiogram* and applied it to the three ECG wave components P, QRS, and T, so obtaining, respectively, the P-, QRS-, and T-loops. However, the procedure was tedious and inaccurate (the paper has an interesting figure) and Mann attempted to use the then relatively new cathode ray oscilloscope, but the technology of those days was not satisfactory [40]. Sixteen years later, in 1936, Schellong reported the successful use of the oscilloscope for automatic recording of heart signals.

Wilson et al. [41]–[43] suggested, in 1938, the name *vectorcardiogram* as more descriptive than the term monocardiogram. The latter paper by Burch [43] is comprehensive and clearly describes the development of the cardiac vector concept. The circuit arrangement applied by Wilson et al. in 1938, using an oscilloscope, was used to achieve a Lissajous-like loop. The main difficulties faced by vectorcardiography were, first, to obtain three orthogonal leads with the least time delay among them and, second, the high cost of the equipment involved. Several lead systems were proposed but there is no question that Frank's arrangement in 1956 was the best [44]. However, for decades, the equipment stood as the biggest obstacle in the way of its enhancement and usage. Other contributors to the subject were Hollman and Hollman [45] in 1939.

Dower [40], in 1980, proposed a mathematical transformation to obtain the vectorcardiogram (VCG) from the ECG and vice versa, thus opening the path for carrying out both kinds of studies using single equipment. Later on, several investigators came up with similar transformations, such as Kors et al. [37], in 1990 and Guillem et al. [38] in 2006. In addition, many technological improvements in the ECG machines, including rather low-cost, high-resolution digital acquisition units, allowed for easier and better determination of the VCG by simply applying a transformation to the ECG records (Figure 3). Along with such significant advances, the VCG has been studied in patients with different types of heart disease in an effort to evaluate their cardiac risk. In other words, the VCG became (or is becoming) a truly practical and reliable clinical tool. The following stages can be distinguished in this respect, all rather recent (as time seems to compress when viewed in a historical perspective).

1) Early in the VCG studies, an oscilloscope screen was used to project the three classical planes (frontal, horizontal, and sagittal). Their careful analysis, according to Wolff [39], would evaluate changes during ischemia or infarction more accurately than the regular ECG pattern.
2) In more recent studies, several researchers have developed different techniques based on the VCG to study cardiac diseases. Bortolan et al. [50] proposed myocardial ischemia characterization from the T-loop morphology defining some parameters. Nowinski et al. [51], in turn, detected changes in ventricular repolarization during coronary angioplasty by observing that the T-loop morphology is more sensitive to coronary occlusion than the QT-dispersion [51], while Rubulis et al. [52], part of the same research team, used the T-loop morphology rather than the T-vector angle to separate coronary acute diseased patients from healthy subjects.
3) An alternative vectorcardiographic analysis has been carried out through the study of a few indexes, such as the QRS-vector difference (QRS-VD), ST vector magnitude (ST-VM), and ST change vector magnitude (STC-VM). Even though these studies are not directly related to the VCG, several authors have used them to study acute myocardial ischemia and infarction. For example, early continuous QRS-VD and STC-VM monitoring in patients with acute ischemic heart disease may predict the results from an exercise test offering prognostic information. Furthermore, this VCG monitoring can be used to identify myocardial reperfusion at an early stage and give valuable prognostic information in patients with unstable angina [53], [54]. Dellborg et al. [55] concluded that monitoring of QRS- and ST-vector combinations may be a highly sensitive method for detecting myocardial ischemia.
4) Finally, and to update a little, the authors very recently used a set of vectorcardiographic QRS-loop parameters, combined with STC-VM computed in resting records, to distinguish ischemic patients before undergoing percutaneous transluminal coronary angiography (PTCA) from healthy subjects. After a classification process via discriminant analysis, it was concluded that this combination improved the sensitivity and specificity values with respect to those obtained using only the STC-VM index [56].

### *Ventricular Gradient*

This concept was introduced by Frank Norman Wilson (1890–1952) in 1934, who believed that cardiologists would obtain from it clinical information not possible by other means [57]. Among other contributions, he also proposed the Wilson Central Terminal (WTC) of ECG. Simply stated (and this is important):

> The VG is the net electrical difference between the area enclosed within the QRS-complex and that within the T-wave, as produced by the ECG record. It may be said also that it is the net electrical effect of the differences in the time course of the depolarization and repolarization processes; they can be expressed as a mean

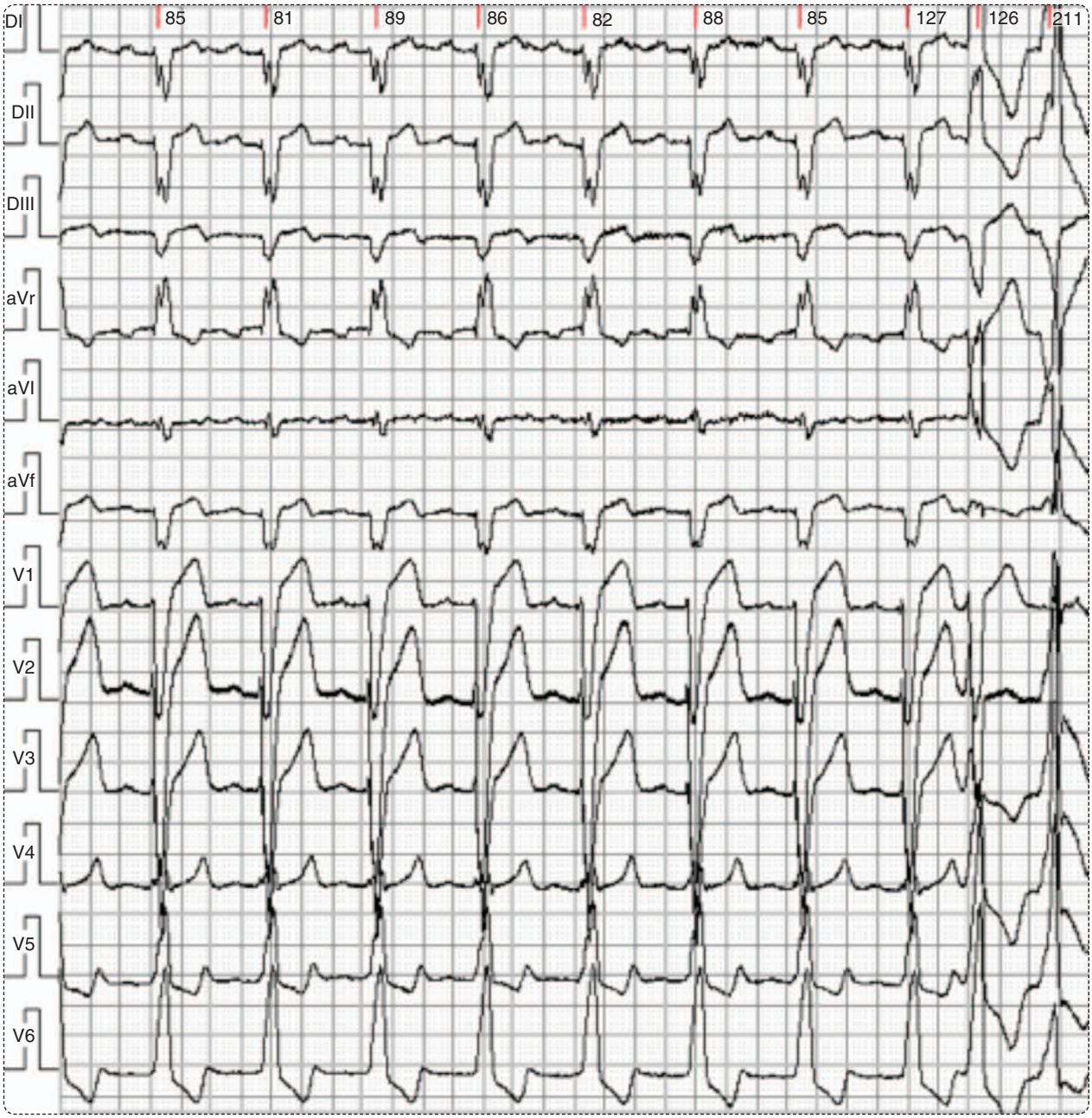


**FIGURE 3** The simultaneous digital 12-lead ECG records. The records were taken by one of the authors at the IIBM-UBA using ECOSUR-SA equipment (Buenos Aires, Argentina). The vectorcardiogram is easily derived by a mathematical transformation, as explained in the text.

> vector. Still in another wording, the ventricular gradient is a single vector quantity which defines the mean difference in magnitude and direction of the excited state duration and the electric potential recovery for the entire electrical ventricular beat.

In humans, the normal heart presents a ventricular gradient (VG) of significant magnitude, whose direction is determined by the anatomical position of the heart. Several physiological factors generate metabolic heterogeneity, which heavily influences the depolarization and repolarization pathways, hence leading to specific VG [58].

Computing the VG allows for the analysis of several ECG abnormalities, such as hypertrophy and conduction deficiencies, among others. In spite of these potential advantages, Wilson's idea was not accepted, mainly due to two reasons: first, the concept was difficult to grasp and, second, its use required too much time [59], [60], which, by and large, physicians cannot spare. In the original 1934 paper by Wilson et al. [57], the authors clearly state:

> It is the purpose of this article to describe a method of analyzing the electrocardiogram, which has not been employed heretofore and which yields information not obtainable in other ways.

In fact, they did believe in it; their previous results had been communicated in 1930 and 1931, as they mentioned in a footnote of the 1934 paper. Not many

understood the concept of VG, and it took nine years for someone to recall it; Bayley and Monte [61], in 1943, applied VG to acute myocardial ischemia. At almost the same time, Ashman et al. [62]–[65] published four tutorial papers where the concept was described in detail along with the methods of calculation, but without triggering much response from the medical community. Later on, in 1945, Burch and Winsor [66] published a book in which the new idea was included; however, in spite of the excellent figures and good didactics, the book could not develop further interest. Other authors also dealt with VG, including Cabrera et al. [67] in 1947. Barker, one of the coauthors of Wilson's initial paper, wrote a book in 1952 [68]; in it he says:

> At the present time, the determination of the ventricular gradient is not a practical procedure for general use in electrocardiography. The theoretical foundations upon which it rests, however, are of utmost importance.

The latter paragraph seems somewhat contradictory and gives an impression of doubt.

By the end of 1940 and into early 1950, Grant [69] further developed the vector concept in ECG, although his book appeared much later, in 1957. His studies were based on the aspects of Wilson's VG using the vector concept in the routine analysis of the ECG signal. In addition, Burger et al. [70] proposed a mathematical analysis of the VG. Other significant papers followed in 1978, 1979, and 1983 [71]–[73]. Finally, in 1999, and making use of the ever-increasing computational power, Wilson's VG concept was revived to calculate the angle between the QRS- and T-loops within an optimal orthogonal three-dimensional space [74]. This new descriptor, called the Total Cosine R-to-T, proved to be a good cardiac risk predictor [75]–[78]. In conclusion, the VG concept is, indeed, an effective tool of cardiac risk assessment. Its development, like that of many other subjects, has been painstakingly slow. Still, it needs to establish itself more firmly.

### *High-Resolution Electrocardiography*

High-resolution electrocardiography (HRECG) is defined as the computerized recording of cardiac electrical activity oriented to detection and analysis of micropotentials not visualized in the conventional ECG [79]. This technique, based on digital processing, is characterized by a greater resolution in the amplitude and frequency scales. Often, it is also called high-fidelity ECG. The minimum sampling frequency is in the order of 1,000 Hz with a resolution equal to or better than 12 b [80]. Figure 4 shows typical records.

The beginning of HRECG can be traced back to the 1970s, when trying to noninvasively detect His-Purkinje system activity. In 1973, Berbari et al. [81] reported for the first time the combined HRECG with coherent averaging in experiments carried out in dogs. Almost simultaneously, other investigators applied similar procedures for the recording of the same micropotentials [82], [83]. From its very beginning, the ECG microvoltage pickup faced many difficulties due to apparent overlapping of the P-wave final portion and the initial piece of the His-Purkinje complex. However, in spite of these problems, the technique would permit later the detection of other cardiac potentials, especially the so-called ventricular late potentials (VLPs), which show extremely low amplitudes (a few $\mu$V) and high frequency content (25–300 Hz), all them localized in the final QRS-complex and at the beginning of the ST-segment.

In 1978, Josephson et al. [84], [85], making use of programmed stimulation techniques by means of ventricular catheters, were able to clearly detect VLPs in human subjects. Thereafter, other electrophysiological studies determined that the appearance of such potentials was directly correlated with the risk of ventricular tachycardia and, eventually, with sudden cardiac death due to late activation of ischemic regions around a necrotic area; all this can easily give rise to reentry mechanisms [86], [87].

One need that emerged immediately after the first electrophysiological findings was how to detect VLPs using noninvasive techniques. Until then, only intracavitary records were available. In 1981, Rozanski et al. [88] showed that it was possible to detect VLP in humans from surface thoracic records. Nonetheless, such detection is still rather complex due to very low amplitudes; they are masked by noise. Besides, the noise spectrum overlaps with the VLP frequency components, preventing the use of conventional filters. Historically, temporal coherent averaging has been the best way to improve the signal-to-noise ratio. This technique, based on the hypothesis of stable and reproducible VLP (which may be challenged) and accepting that noise is random and not correlated, consists of averaging a set of previously recorded and aligned beats. Its outcome is called signal-averaged ECG (SAECG).

Simson advanced one step further in 1981, as he proposed an automatic method to detect and analyze the VLPs starting from SAECG [89]. The main aspects to underline in his contribution are: 1) use of bidirectional filtering in the three orthogonal leads; 2) combination of these filtered leads in a vector magnitude; and 3) definition of temporal parameters for the detection of VLPs. This paper, along with a few changes, set the basis for VLPs detection in the temporal domain, which is illustrated in Figure 4. Figure 4(a) shows an XYZ-lead temporal segment of the continuous HRECG record from a patient with VLPs. After applying the QRS detection and alignment and averaging algorithms of sinus beats, an SAECG record was obtained [Figure 4(b)], which has a better signal-to-noise ratio than the original HRECG. The individual signal-averaged XYZ leads are thereafter filtered to emphasize the high-frequency micropotentials and attenuate the low-frequency components (P- and T-waves). Often, a bidirectional, 40–250 Hz, fourth-order, Butterworth band-pass filter is used. The filtered $X_f$, $Y_f$, and $Z_f$ leads [Figure 4(c)] are combined into a vector magnitude [Figure 4(d)], where VLPs are finally detected through three temporal parameters.

With Simson's work as a reference, several investigators searched for optimal values of the different parameters employed in temporal VLPs using SAECG. Hence, although numerous papers were published between 1981 and 1990, they were not comparable because they used different cutoff frequencies and abnormality thresholds. As a result, VLP diagnosis in the same patient could be positive with one algorithm and negative

with another. Such discrepancies led the three main international societies (The European Society of Cardiology, American Heart Association, and American College of Cardiology) to form a task force committee in 1991 to standardize VLP's recordings with SAECG [80]. In 1996, another task force committee recognized the clinical usefulness of HRECG and SAECG in cardiac risk evaluation of several conditions, including infarct, ischemia, and arrhythmias [90]. More recently, the same techniques have been applied in patients with Chagas–Mazza disease (an unfortunate pathology plaguing all of Latin America) [91].

## Discussion

We have tried to describe, as much as possible, the relatively recent historical development of cardiac risk assessment, which started with serious quantitative steps in the middle of the 20th century, not more than 50 or 60 years ago, and is part of a much more complex effort aimed at health risk assessment. Advances in science and technology appear at shorter intervals as time proceeds, in some kind of relativistic compression effect. Obviously, mathematics, signal processing techniques, and computers constitute a tripod on which such efforts stand, without leaving out the absolutely indispensable medical knowledge and experience along with reliable statistical data.

Cardiac fibrillation, both ventricular and atrial, should perhaps be considered as probabilistic phenomena that can be biased according to the pathophysiological condition of the subject. Attempts in this direction have so far been few and vague, and models based on chaos theory, up to now, have been disappointing, even though, at one point in time, the theory sounded appealing, and many papers were produced [92]. Some people have suggested game theory as another possible tool, especially after the contributions of John Maynard Smith (1920–2004), a British theoretical biologist and geneticist who started as an aeronautical engineer during World War II. However, nothing has even been suggested in terms of cardiac risk evaluation. Genetics, in this respect, is perhaps more promising, for certainly there are cardiac diseases that can be traced back to abnormal

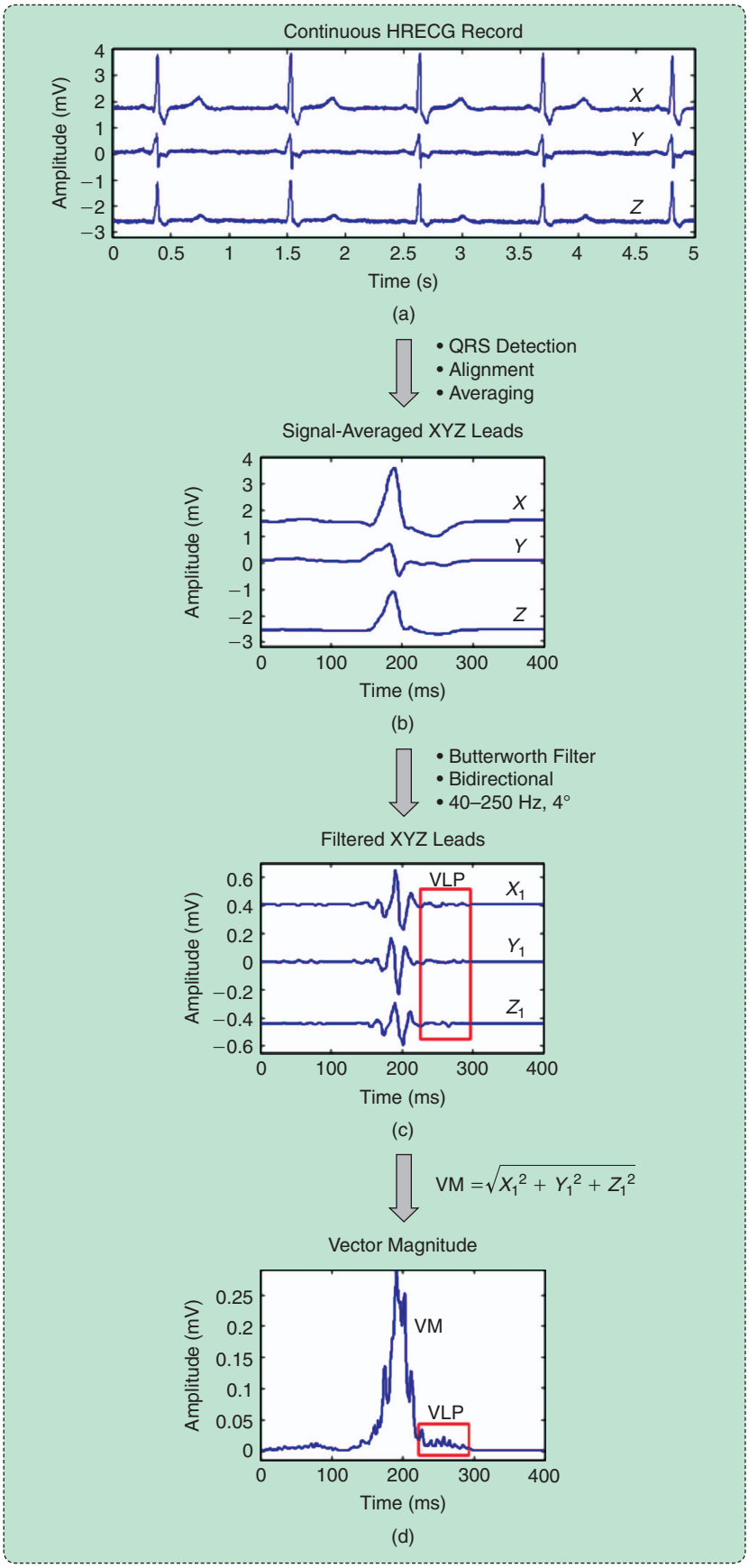


**FIGURE 4** The temporal analysis of VLPs in signal-averaged ECG records. (a) Continuous HRECG record. (b) Signal-averaged XYZ leads. (c) Filtered XYZ leads. (d) Vector magnitude.

chromosomes or gene defects. Biologists often refer to multifactorial inheritance, meaning that "many factors" are involved in a birth defect.

Cardiologists make use of thrombolysis in myocardial infarction. This is a purely empirical predictive score introduced by Eugene Braunwald in 1984, applied to assess the risk of death and ischemic events in patients experiencing unstable angina or a non-ST-elevation infarction. Details can be found on the Internet. Finally, medical imaging seems to come to the front, for its possibilities are numerous and are already being used [93]; these technologies have a lot to offer in terms of health risk assessment.

## Conclusions

There is no doubt that health and cardiac risk assessment and predictions have entered into a quantitative stage, but the error bands are still wide and the road ahead is quite hard. It becomes appropriate to repeat what Philip James Bailey (1816–1905), an English writer, said in *Festus* (scene V, A Country Town), quoted also by Lindstedt and Calder [33] in 1981:

> We live in deeds, not years;
> in thoughts, not breaths.
> In feelings, not in figures on a dial.
> We should count time by heartthrobs.
> He most lives, who thinks most,
> feels the noblest, acts the best.

Wise, deep words to think about, not much different than the quotation given in the section "Allometric Model: An Old Concept Revisited in Cardiology." Lindstedt and Calder had insight and human perception, indeed.

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