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The labyrinth of nomenclature in Cardiology. Eternal dilemmas and new challenges on the horizon in the personalized medicine era

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'*Stat rosa pristina nomine. Nomina nuda tenemus*'

(The ancient rose remains by its name, names only are left to us)

From 'The name of the rose' by Umberto Eco

Introduction

The quest for accurate terminologies and classifications is a constant source of dilemmas in medicine and science and a particularly topical and controversial subject in the field of cardiovascular diseases.

The Cardiology community is torn between the concept of personalized medicine and ambiguous diagnostic categories, often describing non-entities. The debate on what are the best classifications is ignited by the exponential increase in knowledge which parallels with a constant rising in complexity. The intent to capture the intrinsic either physiological or pathological features of each individual may clash with the need to categorize as no classification can represent the complexity of reality beyond a certain extent.

In this viewpoint we will discuss how terminology and classifications evolved in the field of cardiovascular diseases and what are the main nomenclature deadlocks. We will start from the philosophical basis of this enduring debate to eventually approach practical dilemmas, using the example of cardiomyopathies and heart failure (HF).

Terminology and classifications. A long philosophical journey

Terminology invokes the language labels attached to a concept, a constant source of dilemmas throughout the history of philosophy, science and, of course, medicine. The debate on terminology and classifications date at least to the fifth century BC.[1] Plato dedicates a significant proportion of his dialogues to the so-called 'theory of forms' or 'theory of ideas' attempting to answer the major question 'what is the essence of things?'. He supposed that the object was essentially the form and that the phenomena (φαίνω: to appear) were shadows mimicking the form [the discrepancy between essence and phenomena is described vividly in the allegory of the cave (Republic)].[1]

Aristotle interpreted reality in a more empirical way. He introduced the notion that abstract concepts represent descriptions of things that have been classified by describing their attributes. He introduces the idea of categories which refer to qualities. This position rejects the Platonic extreme realism and establishes the view of a universal as being that of the quality within a thing and every other thing individual to it. A substantial form is the essence of a substance and since only universals are definable, substantial forms are universals.[2]

During the Middle-Age several philosophers and theologians (William of Ockam, Roscellinus and others) rejected realistic theories and embraced nominalism. While Plato's (and Platonist) view was that different objects are the way they are, in virtue of the existence of a universal, according to nominalism, only particulars exist and they stem from our representational system or from our language (the way we speak of the world). Human conventions tend to group objects or ideas into categories, which exist because we decide to name them and not because there is a universal abstraction.[3]

More recently Immanuel Kant postulated that universals are not real, but are ideas in the mind of rational beings, fundamental categories of pure reason intrinsically linked to the rationality of the subject making the judgment.[4] The 20th century philosopher

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Ludwig Wittgenstein focused his work mainly on the relationship between language and reality, acknowledging the great limitations of terminology which is highly dependent on the context and assumes a private meaning which is understood differently by individuals involved in a conversation.[5]

It is on the ground of this long and enduring controversy that modern taxonomy was first developed in the 16th and 17th century, a long way before the 20th century era of clinical descriptions, such as Standardized Nomenclature of Diseases (SND) and International Classification of Diseases (ICD).
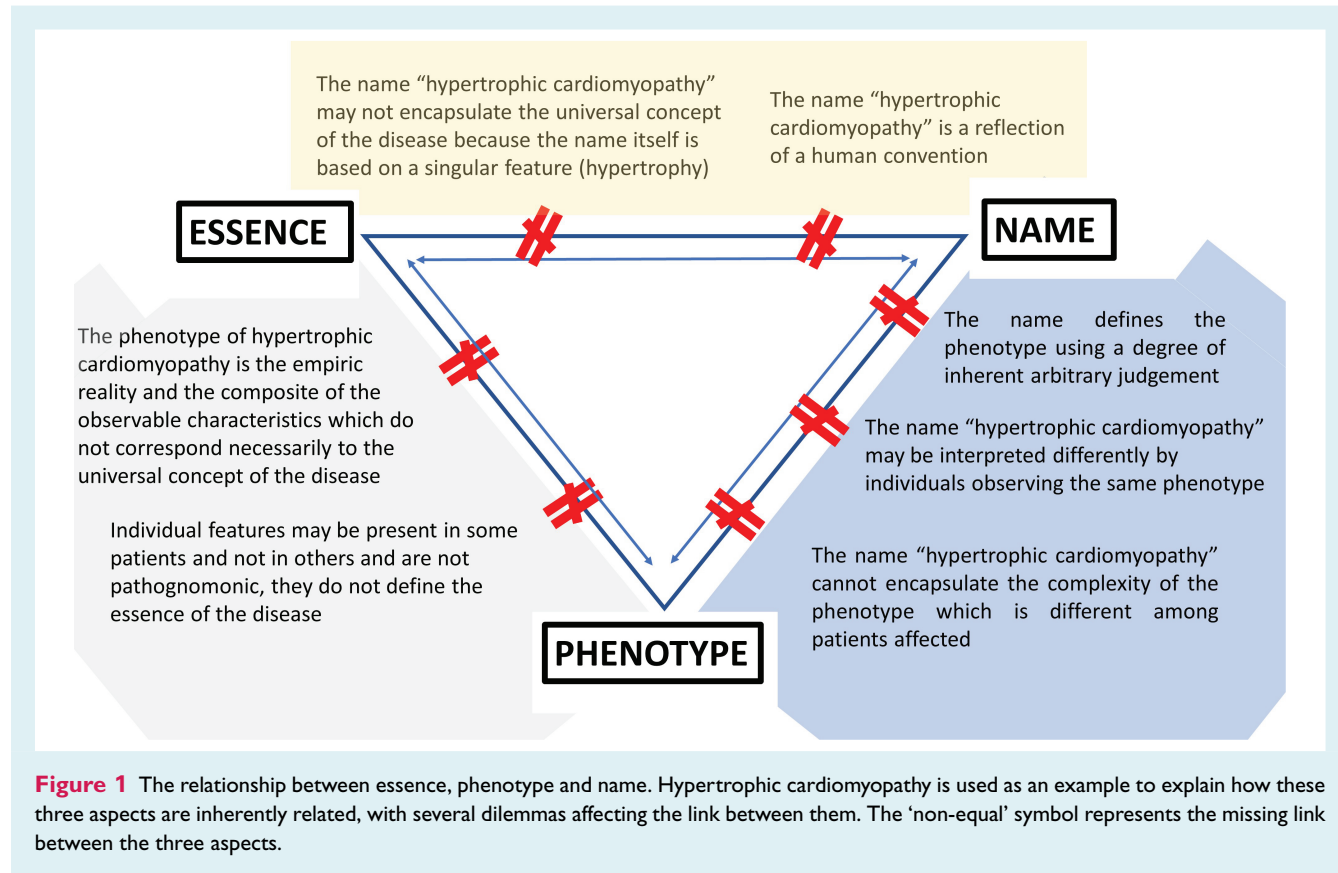
The case of cardiomyopathies

Several definitions and classifications have been proposed in the attempt of capturing the multifaceted nature of cardiomyopathies.[6,7] Specifically, the European Society of Cardiology (ESC) proposes a classification that supports an empiric approach based on phenotypic expression.[7]

The development of these classifications represents laudable efforts that surely provide some clarity in the field. Classifications utilize categories and names that should cover the variable expression of a cardiac condition encapsulating the true essence of a specific disease. Several examples may be used to describe the intrinsic failure of this assumption. The name 'hypertrophic cardiomyopathy' (HCM) suggests a pathological process characterized by hypertrophy of the heart. We increasingly encounter situations where features highly suggestive of HCM are present, such as for example lateral deep T-wave inversion, or family history of HCM, but the wall thickness is measured 11 or 12 mm at the left ventricular apex (not exceeding the threshold of 15 mm as per international guidelines[8]). If we interpret guidelines and the value of the name rigorously, we would probably hesitate to call the aforementioned condition HCM (*Figure 1*). Post-mortem interpretation of cardiac findings in decedents of sudden death with (or without hypertrophy) offers similar challenges[9,10]: some suggest that HCM may be diagnosed without hypertrophy, but with significant myocardial disarray (a profound derangement of normal myocyte alignment at histology); conversely unexplained hypertrophy in the setting of sudden death may not be considered in the same disease spectrum of HCM.[11]

The same can be said of other cardiomyopathies. The name 'arrhythmogenic right ventricular cardiomyopathy' evokes a condition characterized by arrhythmias and where the right ventricle is *the* affected chamber.[12] Longitudinal studies have shown that although a significant proportion of patients experience arrhythmias, many patients have a very stable course.[13] Moreover, blaming only the right ventricle appears inappropriate as the left ventricle has recently been shown to be affected too (or may be the only chamber affected).

The intrinsic risks of a phenotypic classification (or nomenclature) are to stop the diagnostic quest at the first appearance and to erroneously consider a morphologic trait as a specific disease.

Figure 1 The relationship between essence, phenotype and name. Hypertrophic cardiomyopathy is used as an example to explain how these three aspects are inherently related, with several dilemmas affecting the link between them. The 'non-equal' symbol represents the missing link between the three aspects.

The case of heart failure

A certain degree of nomenclature complexity in HF is almost unavoidable as we are referring to a syndrome and not a disease. The ESC guidelines differentiate between three subgroups, basing this classification on left ventricular ejection fraction: HF with reduced ejection fraction (HFrEF), HF with mid-range ejection fraction (HFmrEF) and HF with preserved ejection fraction (HFpEF).[14] This classification provides clarity, but at the same time suffers from some limitations. The ejection fraction is a feature that does not discriminate aetiologies and a patient with reduced left ventricular ejection fraction may suffer from ischaemic heart disease or from an inherited dilated cardiomyopathy.[15]

Even more causal heterogeneity may be found in the group classified as HFpEF that may be truly considered a 'nosographic trap'. Many randomized clinical trials have shown important results in patients with HFrEF.[14] The same cannot be said for patients with HFpEF.[16] Although the reasons for this disparity are still unclear, a main driver for the unsuccess of clinical trials in HFpEF may be the nosographic chaos characterizing this matter. Indeed, HFpEF is not a description of a clinical entity, but the illustration of a 'non-entity'. The definition 'HFpEF' risks to be superficial mixing a wide range of different clinical entities, each requiring specific treatment. The failure of clinical trials assessing the potential of various drugs in HFpEF may be caused by this terminology deadlock.

The issue of differential diagnosis

In the field of HF and cardiomyopathies, differential diagnosis is inevitably arduous, because different disease entities may exhibit the same phenotype and a specific disease may present different phenotypes. An increasing number of studies attempt to test and compare certain features to demonstrate a practical utility in differentiating A from B. However, this experimental approach is based on a dichotomous and mutually exclusive interpretation of reality and therefore relies on the assumption that A and B are separate entities. However, nature usually does not follow dichotomous rules. An example is provided by the issue of differential diagnosis between physiological adaptation to exercise and cardiomyopathies. We should concede that an athlete may have a cardiomyopathy or that a patient with a cardiomyopathy may be an athlete and the phenotype is a combination of a physiological and a pathological process (Figure 2). Using another example, the assumption that A and B (for example dilated cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy) are two separate clinical entities is a postulate: A and B are different because we arbitrarily and conventionally decide to call them with different names (following the aforementioned nominalist vision).

Future challenges and perspectives

The explosion of 'big data', and the constant developments in science and novel technologies, is impacting (and will impact even more in the next future) not only on our understanding of cardiovascular diseases, but also on classifications and nomenclature.[17]

The dissection of reality to an individual level with the purpose of providing a personalized care will certainly come at a price: our ability to cluster and categorize will become remarkably challenging when the quest for the particular will be taken to the extreme and the infinitesimal, losing the awareness of the universal (Figure 3).

Perhaps this process will be accompanied by a move of the focus from clusters and categories to effects and practical repercussions on clinical management. In other words, nomenclature and categories may become tools which are too infinitesimally detailed and complicated to be handled from a human perspective. This would result in a convergence on only few pragmatic algorithms aimed at
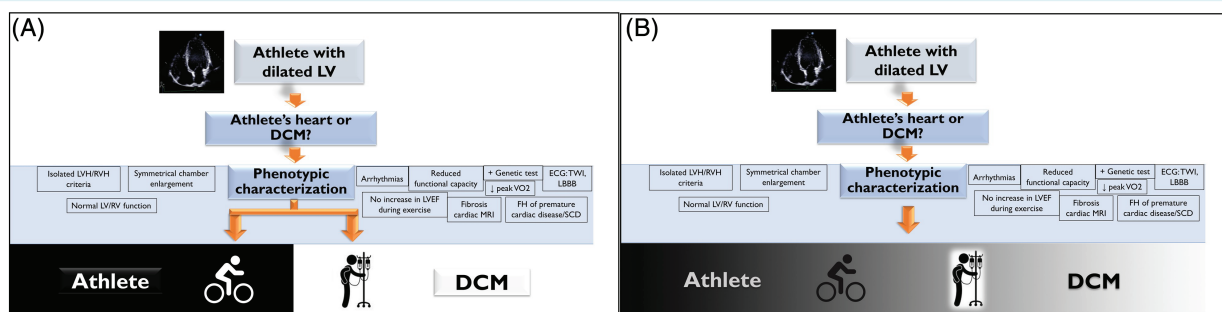
Figure 2 Dichotomous approach to differential diagnosis between athlete's heart and dilated cardiomyopathy (DCM) (*A*). The combination of DCM and physiological adaptation to exercise is possible and therefore an approach based on the recognition of 'shades of grey' rather than a mutually exclusive interpretation of clinical findings would account for the limitations of our knowledge based on empiric reality (the phenotype) (*B*). ECG, electrocardiogram; FH, family history; LBBB, left bundle branch block; LV, left ventricle; LVEF, left ventricular ejection fraction; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; RV, right ventricle; RVH, right ventricular hypertrophy; SCD, sudden cardiac death; TWI, T-wave inversion; VO$_2$, oxygen consumption.
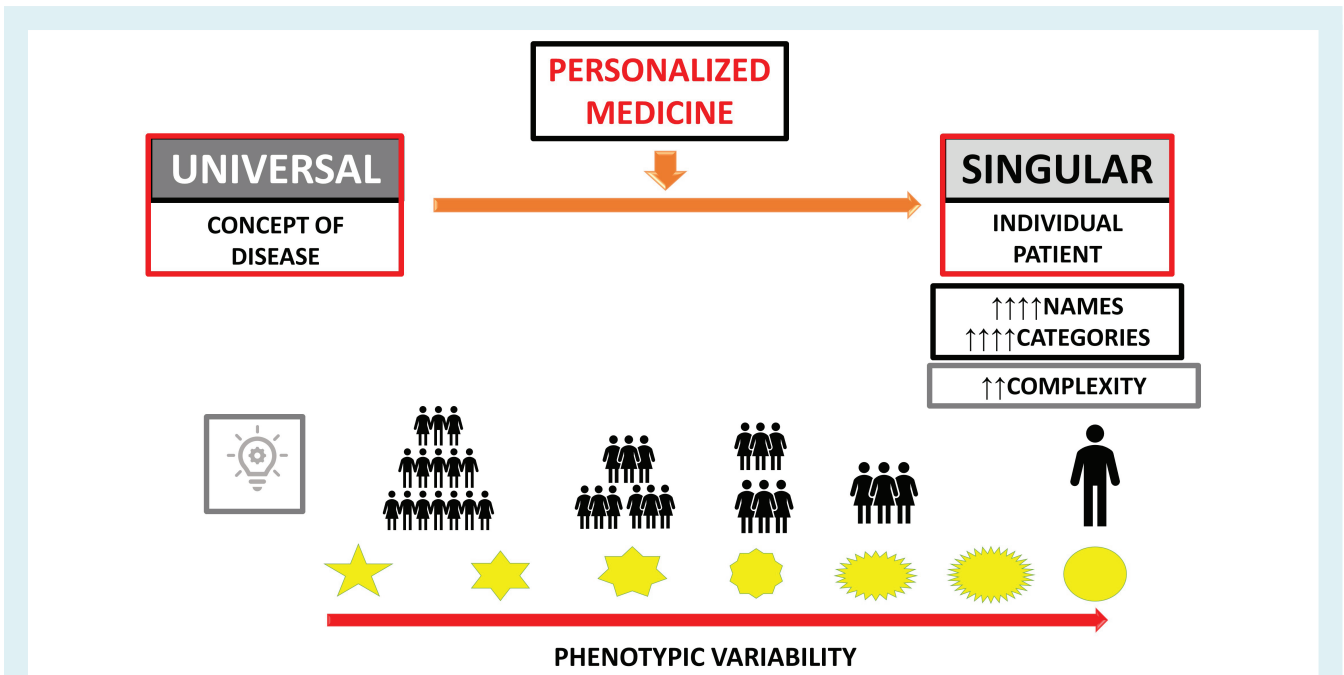
Figure 3 Personalized medicine and raising complexity in definitions and nomenclature. The process of bridging the gap between universal and singular is likely to result in enormous confusion, clashing with the human intellectual capacity to rationalize reality into meaningful categories. The phenotypic variability may be infinitesimally high if one considers the individual patient, rather than categories (increased variability is represented by the increase in geometrical complexity – yellow geometric figures).
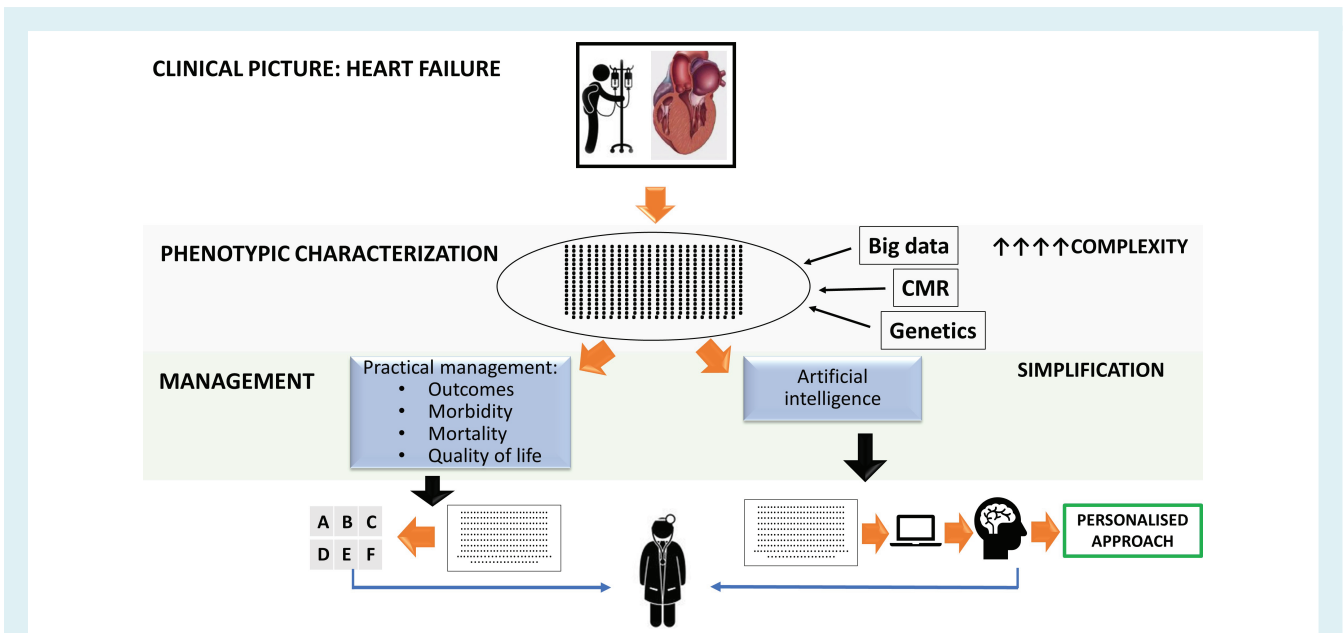
Figure 4 Heart failure may be categorized in a myriad of different disease entities (small dots). Simplification into few major clinical outcomes and focus on practical management may solve the problem of overcomplexity, shifting the target away from categories. Artificial intelligence may enable the clinician to control overcomplexity through a useful interpretation of multiple names and terminologies attached to disease. Nomenclature and complex classifications would gain meaning and relevance if artificial intelligence provides tools to decipher categories as single entities with practical effects which are specific to each single category. CMR, cardiac magnetic resonance.

Table 1 Key messages
1. The field of cardiovascular medicine is becoming increasingly complex, due to our ability to dissect reality to an individual level with the purpose of providing a personalized care.
2. The issue of terminology and classifications is crucial in medicine and extend to other realms of knowledge. From Plato's 'theory of ideas', to Aristotle's 'categories', to the Middle-Age debate on universals and the controversy between nominalism and realism to Wittgenstein's 'private meaning' and incommunicability, nomenclature has been a constant source of dilemmas throughout the history of philosophy and science.
3. Current classifications, especially in heart failure and cardiomyopathies, are mainly based on the phenotype.
4. The possibility to dissect reality to the extreme (for example through advanced imaging and genetics) may overcome a phenotype-focused approach. However, this is an operation that comes at a price with an impact on our ability to cluster and categorize, an exercise that would become remarkably challenging.
5. The issue of intelligibility of an increasing complex reality made by too many categories may be partly resolved by artificial intelligence which may be crucial in simplifying complexity and in creating a framework that may be easily understandable and clinically actionable by the physician.

practical management and at the improvement of major clinical outcomes. Artificial intelligence, which is increasingly penetrating the world of medicine, may offer a different scenario, where computational analysis would allow to rapidly simplify categories multiplied to a great detail and feedback to the clinician in an intelligible form[18] (*Figure 4*).

Conclusions

The debate on nomenclature and terminology is lively in medicine and particularly in the field of HF and cardiomyopathies. Current classifications of cardiovascular diseases are mainly based on the phenotype.

The constant evolution of personalized medicine represents a shift from a 'one size fits all approach' to the tailoring of interventions for prevention and treatment of disease to the individual characteristics of each patient. This paradigm shift will certainly be accompanied by epistemological, ontological and terminological challenges. The eternal problem of universals and of the singular−universal relation, which is a constant theme in philosophy and science, will be magnified to the extreme. Although current phenotypic classifications may be perceived as superficial, empirical and indeed too universal, the ability to dissect reality to the individual will possibly lead to an enormous complexity in definitions and nomenclature, with thousands of different pathological types described. The appropriate balance between extreme complexity and over-simplification will need to be found, possibly introducing artificial intelligence in the process of interpretation of the increasing amount of available information (*Table 1*).

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