**Cardiac Imaging in Heart Failure in the Personalized Medicine Era: Pathway to Knowledge or Tiresias’ Paradox?**

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**Abstract**

Tiresias was the blind prophet of Apollo in Thebes. Tiresias is a symbolic figure, which embodies a paradox: he is blind in the physical sense, but his knowledge surpasses all, as opposed to Oedipus who cannot see despite having a good eyesight. Cardiac imaging can be considered the technological extension of human eyes, which has clearly revolutionised the diagnostic approach in Cardiology and specifically in heart failure. Echocardiography contributed to an approach focused on the ejection fraction (EF) which is the cornerstone of the most recent classifications of heart failure. The recent advances in cardiac imaging raised our ability to understand the aetiological roots of disease. However, the increasing amount of information generated by the plethora of diagnostic imaging techniques raises the challenge of clinical significance. The explosion of “big data” in cardiac imaging may also impact on classifications and nomenclature and on our ability to cluster and categorize, an exercise that is becoming remarkably challenging when the quest for the particular is taken to the extreme and the infinitesimal. The essence of cardiac conditions causing heart failure would probably not entirely captured by an approach only focused on the direct visualization of the heart. Delivery of personalized medicine would not be based only on cardiac imaging, but through an holistic approach which overcomes the mere assessment of empiric reality as it appears to our eyes through the lens of increasingly advanced diagnostic techniques.

**INTRODUCTION**

Tiresias was the blind prophet of Apollo in Thebes. His figure finds roots in Greek mythology and recurs in literature and art. In Sophocles' Oedipus Rex, Tiresias discloses an appalling truth to Oedipus when he reveals him that he is guilty of the ominous crime of killing his father and marrying his mother. Tiresias is a symbolic figure, which embodies a paradox: he is blind in the physical sense, but his knowledge surpasses all, as opposed to Oedipus who cannot see despite having a good eyesight.

Cardiac imaging may be intended as the technological extension of human eyes. With no doubt, the ability to look at heart structure and function has become the foundation of the diagnostic process in Cardiology. The long journey of cardiac imaging has led to unprecedented accuracy in visualization of the human heart with significant improvements in our understanding of the pathophysiology of heart failure (HF) and of the many aetiologies that underlie this complex syndrome1. Despite these extraordinary technological advances, many questions remain unanswered. Although the phenotype looks different through the lens of the most advanced imaging techniques, the issue of significance has never been so challenging, given the raising complexity generated by the very ability to scrutinize reality through detailed visualization.

In the personalized medicine era, the focus of clinical care is on the individual. Similarly, the clinician’s eyes enriched by a plethora of novel technological advances, look at a unique individuality, in the constant attempt to bridge the gap between the singular patient and the complex information deriving from clinical trials.

In this constantly shifting landscape, we discuss the values and limitations of imaging in understanding HF and its underlying causes and in suggesting appropriate treatment.

**The imaging approach in heart failure**

Cardiac imaging is the milestone of diagnosis, classification and management of HF. Although other aspects, such as clinical history, physical examination and natriuretic peptides are crucial in the first phase of suspicion and confirmation, echocardiography is the turning point to enable some understanding of pathophysiology and to plan treatment. Assessment of left ventricular (LV) systolic function and of LV ejection fraction (LVEF) constitutes the basis for current classification. The European Society of Cardiology (ESC ) guidelines differentiate between 3 subgroups: HF with reduced EF (HFrEF) – LVEF < 40%, HF with mid-range EF (HFmrEF) – LVEF 40-49% and HF with preserved EF (HFpEF) – LVEF ≥ 50%2. Medical treatment is based on this classification which provides some clarity3, but at the same time suffers from some limitations. The EF does not provide per se an aetiological characterization, but is the parameter that currently impacts more than anything else on our management strategies. Patients with different aetiologies will receive the same treatment based on the common denominator of the EF; conversely, patients with similar underlying aetiology will receive different treatment based on a different EF. The diagnosis of HFpEF is often challenging as it is a “nosographic box” that groups together various conditions with significant heterogeneity. According to the most recent European Society of Cardiology (ESC) HF guidelines4, demonstration of diastolic dysfunction is required. However the current assessment of diastolic (dys)function with echocardiography is complex and relies on a multiparametric assessment. In this context, novel imaging techniques hold the promise to enable us to “see better” 5,6. Cardiovascular magnetic resonance (CMR), three-dimensional echocardiography, global longitudinal strain, DPD scintigraphy and PET-CT are just some of the current diagnostic armamentarium aimed at bringing to light the aetiological roots of disease processes.

**The aetiological conundrum**

A plethora of imaging techniques raised our ability to shed some light on aetiology of HF, overcoming some of the limitations affecting M-mode and two-dimensional echocardiography. For example, an hypertrophied heart with diastolic dysfunction may be the result of many causes with different mechanisms and possible treatments. CMR provides a step toward a more individualized approach, differentiating between hypertrophic cardiomyopathy, cardiac amyloidosis, hypertensive heart disease or other rarer conditions7. In this context, 99mTc-DPD scintigraphy has been recently found a sensitive non-invasive tool for imaging transthyretin (ATTR) cardiac amyloid8. Similar benefits can be found in the assessment of patients with reduced systolic function: CMR may differentiate with a reasonable accuracy between idiopathic (possibly inherited) dilated cardiomyopathy, ischemic cardiomyopathy or arrhythmogenic cardiomyopathy with predominant left ventricular involvement9; in the context of LV systolic dysfunction, PET-CT may reveal myocardial inflammation suggestive of cardiac sarcoidosis, with significant implications for clinical management.

A wise interpretation of the information deriving from novel imaging techniques challenges an LVEF-centred approach as tissue characterization may orient risk stratification and therapeutic choices, even when LVEF is normal, especially in certain familiar or genotypic contexts. It is important to acknowledge that various levels of vision exist: a superficial one in which images enter the retina and mind and are automatically received (typically the EF), and various further deeper levels in which the final "mental image" is the result of an active interrogation process of reality, hopefully according to a predefined grid. In this way, observation, deduction and culture come together, greatly enriching the result of the initial simple visual inspection.

Despite the many benefits of a detailed tissue characterization using the most contemporary imaging armamentarium, some limitations should be acknowledged. The appropriateness of a certain diagnostic tool should always be considered and possibly questioned if tangible clinical benefits may not be acquired. Moreover and not less importantly, all imaging techniques look at signs and features which need to be interpreted in the patient context and according to what is the “normal” in the population, raising the issue of significance.

**Imaging signs and significance**

Medicine has always used signs to understand the “culprit”, i.e. to make the diagnosis. The perpetual quest for the pathognomonic sign clashes with several limitations, that in modern times appear even greater than in the past. Bayes' theorem suggests that signs interpretation should be contextualized according to the prevalence of the disease in the population, therefore preventing their use in absolute terms. Moreover, the increasing amount of information generated by the plethora of diagnostic imaging techniques raises an additional challenge which may appear paradoxical. While we would expect an excellent diagnostic armamentarium to draw the contours of clinical significance with clear demarcation lines, the differentiation between culprit and innocent by-stander appears softened in shades of grey of uncertainty as never before. For example the finding of mid-wall or subepicardial late gadolinium enhancement in the lateral wall may be a sign of a prior myocarditis, may be suggestive of a cardiomyopathy or may be found in veteran athletes who exercised for decades without reporting any symptom10. An approach based only on echocardiography (as it was in the past) would not capture the scar unveiled by CMR and would be therefore immune from the issue of its significance (and the related impact on clinical management). The ability of distinguishing black and white is becoming increasingly challenging as the number of shades of grey becomes higher, impacting on decision making and clinical management.

**The issue of nomenclature**

Cardiac imaging techniques potential to shed light on aetiology of HF may clash with the changes in nomenclature which are a result of the constant developments in the understanding of cardiac conditions. Cardiac imaging per se combined with other revolutionary approaches, such as genetics, offer a higher degree of complexity which impacts on terminology, classifications and therefore general approach to disease from a theoretical and practical standpoint. By definition, cardiac imaging looks at the phenotype, the sum of observable traits and the visual epitome of empiric reality. A risk that is faced in everyday clinical practice is that imaging techniques may not enable to bridge the gap between a series of features observed in the individual patient and universal definitions (often formulated with a certain degree of arbitrary judgement and certainly based on the amount of literature information available at the time when they are made) that should theoretically capture the essence of diseases. For example, left ventricular non compaction is a cardiomyopathy with a specific nosographic allocation, however increased trabeculations (deviating from normality) may be observed in healthy individuals such as athletes11 or may be physiological during pregnancy and may be even found in other cardiomyopathies such as dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM)7. Similarly, DCM is defined by LV dilatation and systolic dysfunction. However, chamber dilatation may be absent and indeed, the term “dilated” has been recently questioned12. A defining imaging feature may be reduced to trait that may be found just in some cases, losing the prerogative to unveil the essence of a pathological condition. Especially in the context of cardiomyopathies, the genotype may be seen in antithesis with the phenotype. However, the dichotomy between genetic or primary and environment/ lifestyle-related or secondary cardiomyopathy is often inaccurate and artificial, considering that the question “nature or nurture?” does not have a clear answer in many cases. In line with the metaphor expressed in the title, the question on to what extent is the acquisition of a certain phenotype unequivocally determined by the genotype is certainly not new and has analogies with what extent is the behaviour of Oedipus unequivocally determined by fate.

**Future perspectives**

Artificial intelligence (AI) is seen by many as the new frontier in cardiac imaging13. The overall research goal of AI applied to medicine is to create technology that allows computers and machines to function in an intelligent manner. Artificial intelligence and computer algorithms offer exciting perspectives to acquire and analyse enormous amount of data. Machine learning has the potential to enhance our knowledge in cardiac imaging by virtue of significantly reducing the time required for image segmentation and analysis. This process may simplify methods to reach information on large scales of individuals and to draw accurate conclusions on normality and significance of certain findings. The attempts to translate “big imaging data” on the individual patient have the purpose to deliver a medicine which is truly personalized. This goal, which some may consider utopic, should be balanced with the paradox that cardiac imaging may not be able “to see” everything, despite the highest technological standards. The complex field of cardiomyopathies, offer several scenarios where certain ” seemingly prophetic “ variables, such as the family history of premature sudden death or of cardiac disease may be more relevant than what is visualized through cardiac imaging, at least for risk stratification14.

**CONCLUSIONS**

Cardiac imaging has witnessed exponential technological advances in the last decades and has become an essential aspect of Cardiology with relevant repercussions on management of patients with HF. Therapeutic strategies in HF are largely based on echocardiography and specifically on LVEF. Novel imaging techniques have the potential to deliver an aetiological diagnosis which is the basis for a personalized treatment, something that will increasingly characterize future medicine. The development of higher levels of complexity and the plethora of information available may create new challenges where AI appears as a possible solution for rapid analysis and simplification.

Tiresias myth is a reminder that knowledge does not equate empiric reality, which in this context is learned through the lens of cardiac imaging. The understanding of cause-effect relationships in the individual patient, the burden of the non-visible “genetic risk” which is often unveiled by family history and other clinical aspects that go beyond the mere visualization of the heart, may provide an holistic assessment that leads the way toward personalized medicine.

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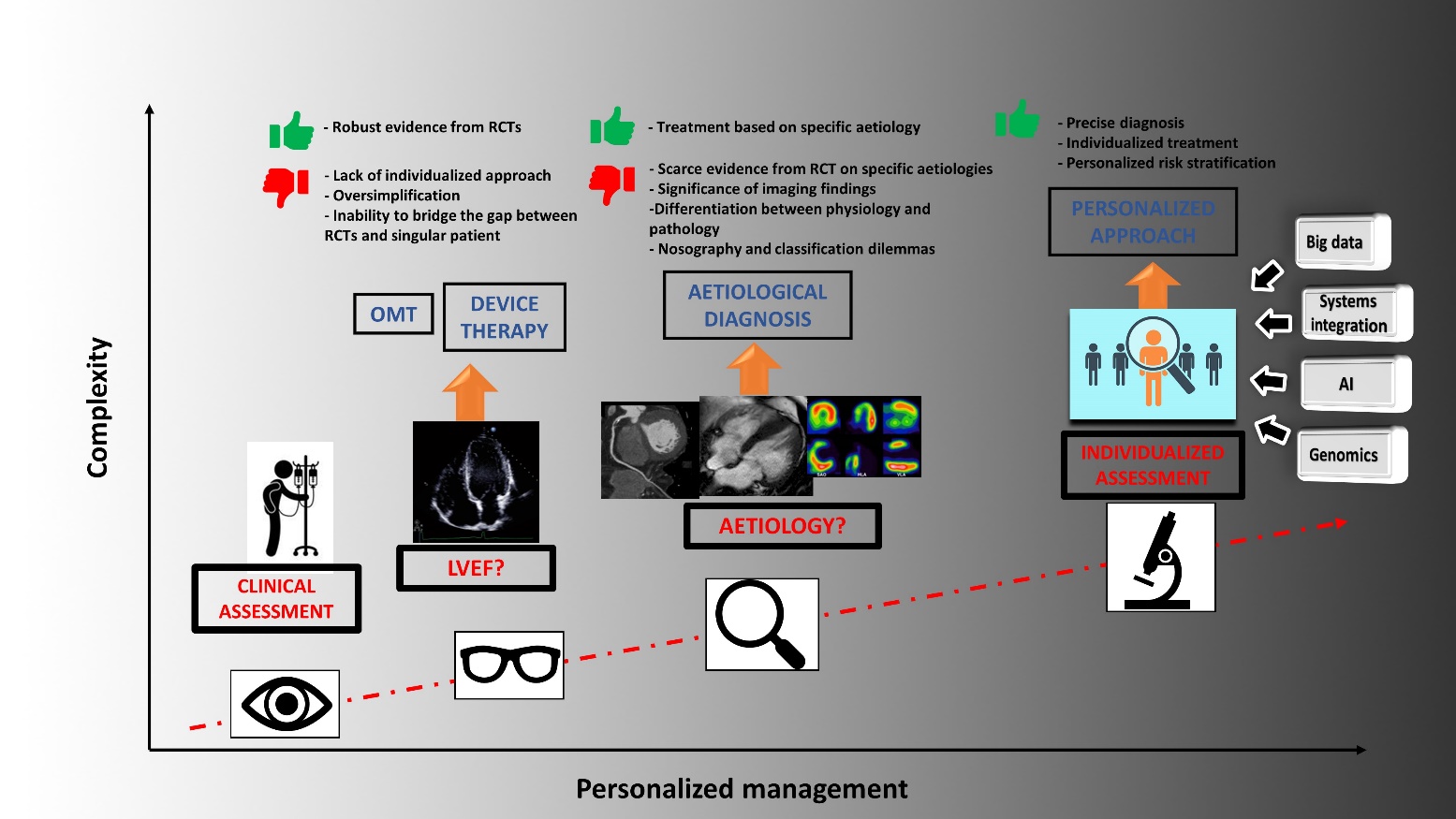
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**Figure 1.** From clinical assessment to personalized management.



**Abbreviations:** AI: artificial intelligence; LVEF: left ventricular ejection fraction; OMT: optimal medical therapy; RCT: randomized clinical trial.