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Every Single Heart

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Abstract:

Randomized trials have always been considered a fundamental step for the validation of a treatment. However, in the cardiovascular setting the results are often nuanced and not very conclusive as they are limited by a wide selection bias and by several confounding factors. Moreover, the result of a study may be affected by parameters not considered, or not completely corrected, that remain as inducers of negative outcome over time. We here propose an alternative method for the identification of the degree of ventricular dysfunction based on the inclusion of many, wellknown, routinely used, echocardiographic parameters. This configures a multi-parametric rating (Heart Dysfunction Rating, HDR) of cardiac function to be used in the framing of a disease (HDR^{pre}) and in the analysis of the post-treatment outcome (HDR^{post}). The HDR can stratify patients in a very capillary way, can be facilitated by a web-based spreadsheet or a smartphone app along with a colorimetric scale or Cartesian graph. The HDR could ensure the application of a treatment to truly homogeneous series of patients and therefore produce a more reliable analysis of the results and their clinical application. It is also in line with a more modern ethical vision in conducting clinical trials.

Keywords: multiparametric assessment, echocardiography, big data system, cardiovascular studies, randomization, rating.

1.Roll the dice

Randomized trials have always been considered a fundamental step for the validation of a treatment. However, in the cardiovascular setting the results are often nuanced and not very conclusive as they are limited by a wide selection bias and by numerous confounding factors. When we study a drug or a surgical correction on the heart, we apply the treatment on an organ that has multiple function/dysfunction and structural parameters, but we hardly consider them all, and not even the majority of them. This means that the result of a study may be affected by parameters not considered, or not completely corrected, that remain as in ducers of negative outcome over time, or sometimes non-homogeneous classes of patients are compared, despite all the precautions in their selection made by clinical investigators.

Some examples from recent literature can clarify these limits.

A patient with ischemic cardiomyopathy is included in a study based just on the ejection fraction (EF) and operated on by ventricular

reconstruction. The EF improves but the volume do not reach a physiologic value and the left ventricular twist does not recover: two important determinants of dysfunction remain after the operation. The endpoint is reached but late outcome is negative. Is the outcome of the procedure due to the procedure itself or to the persistence of conditions favoring a negative remodeling?

A very important study on ischemic mitral valve regurgitation (MR) compares patients treated by means of valve repair (anuloplasty) with those in which the valve was replaced (bioprosthesis). The primary endpoint was end-systolic volume, a well-known major parameter of negative remodeling [1]. Recurrence of mitral regurgitation was one of the secondary endpoints.

The study reported no significant difference in left ventricular reverse remodeling or survival, both at 12 and at 24 months after surgery, but a significantly higher recurrence rate of mitral regurgitation (MR) in the repair group ($p<0,001$).

Reading only these results, we conclude that there is no influence of the two correction techniques on reverse remodeling (primary endpoint) and on mortality, although the repair group has an increase in re-admission rate due to recurrent mitral regurgitation. But a direct comparison of these two correction techniques is not really intuitive, since in the replacement group the recurrence of mitral regurgitation is almost impossible unless there is structural deterioration of the prosthesis (rare at such a short distance of time) or a surgical failure/complication (paraprosthetic leak and/or endocarditis) [2]. In the discussion we find a very important datum: in the repair group, the end-systolic volume in patients who had recurrent mitral regurgitation is 64.1 ± 23.9 mL/m^2 and 47.3 ± 23.0 mL/m^2 in those with competent mitral valve. The endpoint is significantly different but within a single group, among patients who have recurrent mitral regurgitation and those who do not. The recurrence of MR is a factor of negative remodeling and of worse outcome and obviously the valvular repair is the technique that resulted most affected by this complication. But we don't have the exact correspondence between the endpoint values before and after the operation, we don't know which exactly of the ventricles have developed a redilatation. All this makes the study partially interpretable as is: the importance of the primary endpoint is highlighted only within a single group but with high clinical impact and the secondary endpoint compares two "not comparable" techniques. Authors themselves conclude that further follow-up, identification of predictors of recurrence of mitral regurgitation and more appropriate selection of patients was needed.

Another study on ischemic cardiomyopathy [3] with or without left ventricular reconstruction, has even missed one of the primary endpoints, i.e. the volume reduction of at least 30%, achieving an average reduction of only 19%. The effectiveness of ventricular reconstruction cannot be evaluated analyzing these results, however the study concluded that there were no significant difference in mortality and re-hospitalization between the groups with and without ventricular reconstruction. The truth is that none of the two groups had achieved an effective volume reduction, as required by the study protocol, so two groups of patients with similar ventricles were compared in the postoperative statistical analysis. Only the study of the subgroup of patients who had reached the endpoint of 30% volume reduction showed the real impact of the surgical technique on survival and postoperative functional status: those with the greatest volume reduction had better results over time, as was already clear in the numerous observational studies that preceded the randomized one [4].

Other randomized cardiovascular studies report also many cross-overs and often the data in the as-treated series are more indicative than those in the intention-to-treat series [5]. It is as if the most reliable results deriving from these randomized studies are obtained from the "observational" (non-randomized) portion of the patients included. The problem of patient selection occurs several times in the limitations of such studies. Indeed, the cardiovascular system is so

complex that it is difficult to select truly homogeneous classes of patients. In the Gaussian distribution within a group, patients with very different characteristics are included (see the range of values defined by the standard deviation) and moreover the selection often takes place on the basis of a few functional parameters, not of all those that can well identify a homogeneous level of disease. The normal function of the heart depends on many parameters that are hidden in a selection based on a few of them.

The limitations reported in these trials are very important: they often disrupt the use of results in everyday clinical practice; let the individual professionals still rely on their personal experience; limit the validity of the meta-analyzes that try to provide statistical clarity at a higher level, but maintaining the errors of the analyzed studies. Studies with these limitations have "wasted" thousands of patients and treatments, not coming to usable conclusions. The cardiovascular field is so complex that it deserves a critical review of the methods of conducting clinical studies, not relying only on a "roll of the dice" for decisions that can change patients' lives.

2. A stone into the water

The correct and efficient functioning of the heart is linked to many variables, with (at least) these intertwined key areas: chamber geometry (aspect ratio, systolic and diastolic volumes), fibers disposition (multilayered, 3D network), laminar flow (systolic and diastolic with apical vortex), functioning valves (closure competence and no obstruction), sequential conduction (atrio-ventricular and intra-ventricular synchrony), systo-diastolic efficiency, strain (longitudinal, circumferential, radial), rotation (basal opposite to apical) and ventricular torsion [6].

A heart disease affects the various parameters in different ways (and so does treatment!). There are parameters altered before others or differently from others. It is unavoidable, however, that each altered parameter is then added to the others with an incremental negative influence on cardiac function, since the heart is an "anatomical and functional syncytium" [7].

There is no change in volume that does not alter the intra-ventricular laminar flow, there is no valvular stenosis that does not generate myocardial fibrosis, there is no ischemia that does not alter ventricular torsion. We could say that a disease damages the heart like the waves caused by a stone fallen into the water but these waves also come back after hitting the shore and amplify the damage, perpetuating this vicious cycle.

This makes every single heart an entity in itself that must be thoroughly focused to judge its state by means of numerous structural and functional parameters. In this particular setting, patients' grouping can only be done on the basis of multiple parameters and not just a few. This "interlaced" way of functioning of the heart is probably the basis of the limitations of randomized studies. They inevitably take into consideration only a few of the many parameters that define all together the functional status of the heart. Therefore the selection of patients often hides a series of parameters which are then the cause of clinical failures in the analysis of the results.

Studies are often too "sector-based": electrophysiological studies often consider just the aspect of electrical conduction, the surgical ones just the morphological results, the cardiological ones just the therapeutic effects. But the interaction of a resynchronization, a ventricular reconstruction and heart failure drugs with cardiac function and its several parameters goes beyond a simple, one-way, cause-effect modality.

An integrated and multiparametric assessment should guide the heart studies, because it is more suitable for the integrated mode of cardiac function. Today, more and more researchers tend to critically reconsider the statistical significance between mean and standard deviation data in order to obtain a more objective evaluation of the results, avoiding the dichotomous categorization between what is statistically significant and what is not [8].

3 . Heart dysfunction rating (HDR)

We here propose an alternative method for the identification of the degree of ventricular dysfunction based on the inclusion of many related, interlaced parameters. It is a question of listing all the major parameters of cardiac function, known for decades and obtainable just with an echocardiographic examination, and give a weighted score to each different dysfunction level. The echo is the most widespread, bed-side, reproducible way of analyzing cardiac function, enriched in recent years also with 2D speckle tracking for the analysis of left ventricular mechanics and torsion. This leads to a multi-parametric rating (Heart Dysfunction Rating, HDR) of cardiac function to be used in the evaluation of a disease (HDR^{pre}) and in the analysis of the post-treatment outcome (HDR^{post}). Today, we know a very wide list of parameters to be considered to correctly frame heart's status and outline a performance rating of every single heart. The HDR is based on all of them in order to outline a complete picture of cardiac disease and stratify patients in more homogeneous dysfunction classes (Table 1 reports a preliminary proposal).

Table 1: Heart Dysfunction Rating (HDR) table. Example of ischemic dilatation of the left ventricle with severe mitral regurgitation operated on by reshaping of the left ventricle and competent mitral repair (unweighted data).
Grading: 0=normal (white); 1=mild defect (green); 2=moderate defect (yellow); 3=severe defect (red)

Parameter	Dysfunction grading			HDR^{pre}	HDR^{post}
	mild [score 1]	moderate [score 2]	severe [score 3]		
Ejection Fraction (%)	40-54	35-39	<35	3	1
Diastolic function (E/A)	≤0.8	0.8-2	≥2	2	1
Deceleration Time (msec)	>200	160-200	<160	2	1
End-systolic Volume index (mL/m^2)	31-39	40-49	≥50	3	1
End-diastolic Volume index (mL/m^2)	70-79	80-89	≥90	3	1
End-diastolic Diameter (mm)	60-63	64-68	≥69	2	1
Aspect ratio (lenght/EDD, mm)	0.5	0.6	≥0.7	2	1
Synchronization (QRS msec)	120-130	131-150	>150	1	1
Mitral Effective Regurgitant Orifice (mm^2)	≤20	21-39	≥40	3	0
Mitral Regurgitant Volume (mL/beat)	30-44	45-59	≥60	3	0
Mitral Stenosis (mean gradient, mmHg)	3-5	5-10	>10	0	0
Mitral Tenting Area (cm^2)	≤1	1-2.4	≥2.5	2	0
Aortic Effective Regurgitant Orifice (mm^2)	≤10	11-29	≥30	0	0
Aortic Regurgitant Volume (mL/beat)	30-44	45-59	≥ 60	0	0
Aortic Stenosis (indexed area, cm^2/m^2)	>0.85	0.60-0.85	<0.6	0	0
Longitudinal Strain (%)	-15 to -20	-10 to -14	≤-9	1	1
Circumferential Strain (%)	-18 to -20	-17 to -15	<-15	1	1
Radial Strain (%)	30-39	20-29	<20	1	1
Apical Rotation (degrees)	10-12	8-9	<8	1	0
Basal Rotation (degrees)	-6 to -7	-5 to -5.9	<-5	1	1
LV Torsion (degrees)	10-13	5-9	<5	1	0
Flow not laminar	diastole	systole	both	1	0
TOTAL				**33**	**12**

The literature on the meaning of the individual parameters and their influence on the outcome is very broad [major guidelines in 9-17] and already allows to validate a simple and linear score. The parameters, their grading and weighting [18] could however be adapted and integrated according with any new evidence. The number of variables considered (diastolic, systolic, geometric and/or functional parameters) can be expanded to cover the entire set of computable echocardiographic data. The sum of the scores is quite similar to what happens in nature: if the volume expands, it is added to the loss of elliptical shape, the dyssynchrony, the valve continence, etc. that depend on it.

The HDR could be applied to any area (medical, surgical, interventionist) of the cardiovascular setting. This HDR can be used to monitor a disease or can be recalculated after treatment, highlighting the areas in which it was most effective. As an added value, this rating can be facilitated by a web-based spreadsheet or a smartphone app that can return the score based on the data entered. A colorimetric scale or Cartesian graph can integrate the result. The capillarity of the analysis allows to group patients into more homogeneous classes, reduces selection bias and guarantees a more reliable result with a higher prognostic predictive value. The proposed rating can also be applied in a second analysis to patients already included in previous studies, provided that additional data can be retrieved.

Let's return to the example of the study on the correction of severe mitral valve regurgitation. Let's suppose we use HDR based on preoperative values. The standard deviation tells us that the volumes ranged from about 37 mL/m^2 to 90 mL/m^2, ejection fraction from 54 to 29% and regurgitation grading from 23 to 57 mm^2. Therefore we have a series of patients that differ a lot from one another: patients with regurgitation equal to 23 mm^2, ejection fraction equal to 54% and end-systolic volume equal to 37 mL/m^2 have milder grade of disease than their counterparts to the opposite extreme of statistical variability. If we calculate a score for each individual patient (every single heart) including all the parameters of the ventricular function, at the end we would have a more capillary rating of the degree of disease, on which to base a definition of more homogeneous classes of severity. For example, the "best" patient of the cited study would have an HDR^{pre} of 4 and the "worst" of 9, more than double. The more parameters are analyzed, the greater the accuracy in judging the degree of dysfunction. Calculating HDR^{pre} for all individual patients, it would be possible to outline really homogeneous classes of dysfunction to which one treatment or the other can be applied.

For example, let us suppose we identify 100 patients with the same functional characteristics, therefore 100 patients with the same HDR^{pre}: applying to 50 of them a treatment and to the other 50 a second treatment, we will be sure to have applied the two treatments to really homogeneous groups of patients. It is thus possible to analyze the effects of the two treatments on the same level of cardiac disease identified with a multiparametric method, reducing the bias due to the unavoidable inhomogeneity if patients are selected only on the basis of a few parameters. If the patients of the mitral study had also been stratified by the tenting area or the coaptation height, which may be different for the same end-systolic volume, the effectiveness of the repair would have been more predictable. Similarly, by applying HDR to patients in the STICH study we would have stratified different levels of ventricular systolic and diastolic dysfunction both before and after treatment: thus we would have obtained more correct data on the effectiveness of ventricular reconstruction, without waiting for the study of subgroups (subgroups: groups more homogeneous by definition).

In conclusion, the observational analysis of the outcomes of a cardiac treatment on patients framed on a multiparametric basis could give more reliable and relevant results than a randomized study on groups of patients

inhomogeneous for structural or functional characteristics.

4. Nature as a "randomized" big data system

In a sense, nature is already "randomized" since the diseases are "regulated" by so many genetic and environmental parameters and by their interaction, that the distribution in the population can be assimilated to a randomized one. Applying a disease (or a treatment) to people means applying it to an uneven series of hearts which differs in numerous but all determinant characteristics, thus constituting a natural "big data" system. If we deepen the stratification of patients with a multi-parametric selection as the proposed HDR, we can clean the "big data system" of nature to observe the progress of a disease and the outcome of a treatment on an extremely large series. Moreover, the fundamental parameters of cardiac function could become endpoints themselves: why calculate only mortality and not consider volume reduction, or restoration of torsion, or synchrony as endpoints? In this way we could calculate more "events" during follow-up, helping the statistical analysis.

The use of this multiparametric HDR could implement a different way of planning clinical trials [19,20], selecting uniform patients to whom apply different treatments and not randomizing patients still different for specific parameters. Starting from subclasses of functionally homogeneous patients, it is possible to trace precise clinical trajectories and a more reliable analysis of the effectiveness of a treatment.

Several advantages can be summarized: a multiparametric study does not neglect basic parameters, both pre- and post-treatment, bringing to light potential confounding factors; selects a homogeneous population thanks to a deep analysis of dense data system; gives the possibility of performing a reliable propensity score within this wide series; reduces the selection bias.

5. Conclusions

One of our main scientific aims is to see the effectiveness of a specific treatment on a specific disease. In heart disease, where the cardiac function is characterized by the interweaving of numerous, equally important and correlated parameters, we could derive an objective datum for the "single patient" (single "kind of heart") clearing the natural "big data system" at our disposal by means of a multiparametric selection method. This allows to improve the classification of heterogeneous clinical syndromes and not to disperse the efficacy of a treatment. The rigorous and complete observation of the entire set of available data on cardiac function can really lead us to reliable conclusions with high scientific value, without dispersing the therapeutic effect in a still too heterogeneous study population.

This could also lead to a different and more modern ethical approach in the conduction of a clinical study.

Conflicts of Interest: The Author declare no conflict of interest.

Author contribution: The Author MC conceived the idea, examined the theoretical bases, profiled the practical applications and compiled an initial scheme of realization of the described method. Therefore the Author holds the intellectual property of the content of this paper.

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