CONTROVERSY

Should We Modify Follow Up Recommendations for Cardiac Follow-Up of Patients during Oncologic Treatment Using other Parameters in Replacement of LVEF?

Agonist

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Since the initial description of cardiac abnormalities induced by the administration of chemotherapeutic agents there has been a documented evolution of methods to find the evidence of such cardiac dysfunction in the heart. The obvious interest has been, not only to treat, but to perhaps even prevent the cardiac changes altogether.

This is well illustrated thru recent history; in particular with the case of adriamycin toxicity (1-2). One of the first methods suggested early on this evolution (1974) was the combination of ECG and chest X Ray films in conjunction to phonocardiography and carotid pulse tracing with serial photography used to describe the ratio of pre-ejection period to left ventricular ejection time (3). Shortly after, in 1976, a new non-invasive method was described using sphygmo-recording of the pulse wave delay (4). Ultrasound imaging quickly followed in a report from the pediatric population (5).

Once cardiac imaging was established in the late 70's and early 80's; a number of publications supported the different modalities available (5-8). It is then; fair to say that early in the decade of the 1980's left ventricular ejection fraction (LVEF) was recognized as the traditional method for initial and follow-up evaluation of ventricular function during the administration of cardiotoxic chemotherapeutic agents.

At the time the most developed modality, and what was considered the gold standard for the evaluation of LVEF non-invasively was radionuclide angiography. A look into the literature of that time will clearly reveal a chronological and timing advantage of the nuclear imaging modalities. LVEF by radionuclide proved to be sensitive, specific, reproducible and in at least one early report a predictor of early toxicity when used with stress (9). LVEF, as a single measure, was clearly the real strength of this imaging technique.

It took years for echocardiography, as an imaging method, to parallel the accuracy values that nuclear tests had so well displayed. After all, it was in 1979 when the LVEF by two dimensional echocardiography methods started to be established and compare favorably with radionuclide ventriculogram imaging (10, 11).

Two dimensional echocardiography imaging has come a long way in the last 2 decades; and the equipment available has improved significantly with the advent of harmonic imaging and systems now able to achieve greater temporal and spatial resolution. The use of second harmonic imaging (12) as well as the use of echocardiographic contrast (13) increased the accuracy of LVEF measures of two dimensional echocardiography to levels comparable with the previous standard in the late 1990's.

Most recently, 3D echocardiography has been recognized as another method for LVEF measurement that compares favorably with the very reliable modality of cardiac MR (14). And in a very recent report of breast cancer patients treated with doxorubicin and trastuzumab, real time 3D echo LVEF showed to be feasible, accurate, and a reproducible alternate imaging modality for the serial monitoring, compared with conventional MUGA (15).

Despite the values of such a measure of systolic function, LVEF has its several clear limitations and it never has been the only measure of systolic performance. Its limitations not only include the always present image quality concerns that still remain an issue on ultrasound imaging, or the technicality of the measure (single beat, operator experience, etc). The ejection fraction is merely the product or amount of relative volume ejected in systole as best measured.

That said, we all know well there are many examples of significantly morbid, progressive, cardiac disease processes where documented changes at the tissue or metabolic level exists in early and even fairly advanced stages of the disease during which time the LV ejection fraction can still be measured as normal or preserved. Diabetes, coronary disease, amyloid, hypertension, age-related diastolic dysfunction can serve as known examples for this.

New methods for reliable non-invasive evaluation of systolic function such as speckle tracking imaging are now available. Speckle tracking imaging has

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helped in the evaluation of some of these disorders just mentioned. Case in point; in a recent study of 114 patients with type II diabetes with controlled blood pressure and without history of heart disease, Ernande (16) and others, using longitudinal strain measures found that systolic strain alterations were present despite normal diastolic function, indicating that diastolic dysfunction should not be considered the first marker of a preclinical form of diabetic cardiomyopathy, challenging a decades old notion.

Several, similar reports now have been published in the cancer population receiving cardiotoxic agents and the use of this particular new technology in the realm of toxic cardiomyopathy has been very exciting . Hare (17) first reported that changes in tissue deformation, assessed by myocardial strain and strain rate are able to identify LV dysfunction earlier than LVEF in women undergoing treatment with trastuzumab for breast cancer. More recently, 2 reports in 2011 have confirmed comparable interesting findings. An example of this is illustrated in Figures 1 and 2.

A group led by Dr. Scherrer-Crosbie (18) with the collaboration of other institutions, including ours, found the cooperative use of troponin and longitudinal strain measures to predict the development of cardiotoxicity in patients treated with anthracyclines and trastuzumab, as defined as a reduction of the left ventricular ejection fraction (LVEF) of ≥ 5% to < 55% with symptoms of heart failure or an asymptomatic reduction of the LVEF of ≥ 10% to <55%. In this study, patients who demonstrated decreases in longitudinal strain measures or elevations in hypersensitive tro-

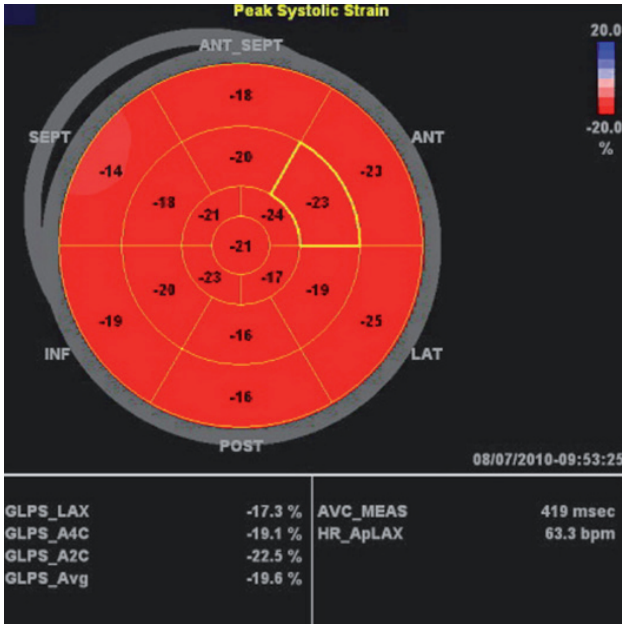

Fig. 1. As an example of our use of longitudinal strain measures this belongs to a 62 year old woman with breast cancer in our clinic; with a normal longitudinal global strain value on 8/7/2010; GLPS = 19.6%. This was after 4 cycles of FAC chemotherapy, but preceding Herceptin. The patient was on lisinopril for pre-existing hypertension. AT this time the LVEF using bi-plane MOD was 55%.

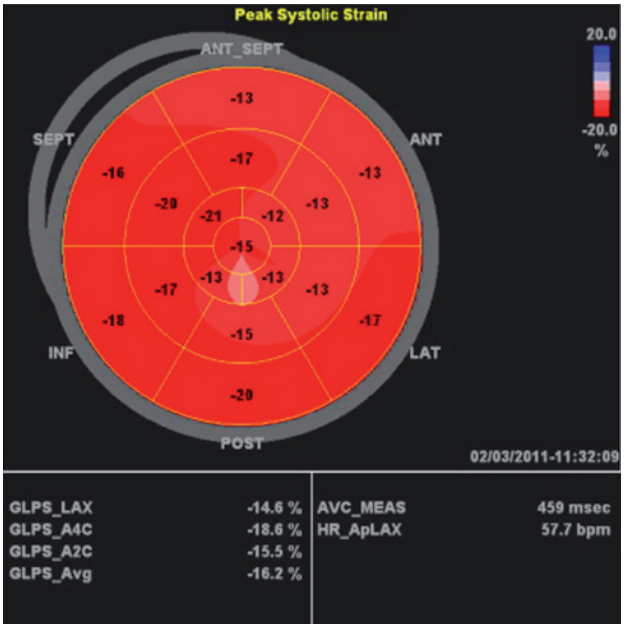

Fig. 2. The same patient, now with a lower global longitudinal systolic strain value on 2/3/2011; GLPS = -16.2% , 6 months into Herceptin. The LVEF at this time was also 55%.
A follow-up echo 4 weeks later showed a LVEF of 45%

ponin had a nine-fold increase in risk for cardiotoxicity at 6 months compared to those with no changes in either of these markers. Furthermore; LVEF alone, diastolic function parameters, and N-terminal pro–B-type natriuretic peptide did not help predict cardiotoxicity.

In a smaller study, Dr. Fallah-Rad et al. (19) reported that tissue Doppler-derived indexes recorded at the base of the lateral mitral annulus TVI and strain parameters did allow for the early detection of subclinical cardiac dysfunction before conventional echocardiographic parameters also in breast cancer patients receiving trastuzumab. In their study only the S' velocity was able to identify all patients who developed trastuzumab-mediated myopathy. Their study also included the use of cardiac MR. With magnetic resonance they were able to show that in patients who developed cardiomyopathy the LV volumes were increased with a subsequent decrease in LVEF at 12 months of follow-up and all these patients demonstrated delayed enhancement of the lateral LV wall. The study was limited however by its size, 10 of 42 patients demonstrated the early changes in TVI and strain. Consequently they recommend a larger population study with longer follow-up. The case of trastuzumab is particularly interesting, since from early on was believed to be a reversible phenomenon; however that idea has come into question (20).

In our cardiology clinic in MD Anderson we have been very conscious of longitudinal strain measures as a tool to recognize early changes. We have used the drop of 10% or more in global longitudinal strain as the alert to consider anti-remodeling therapy and to start the close clinical follow-up and close contact with

the oncologist.

In summary, cancer therapies continue to present cardiac toxicity challenges. The idea that only with LVEF we could detect and later follow these patients, when some patients are now surviving for decades, seems now a situation primed with true promise for improvement. New imaging technologies such as speckle tracking are seemingly ready to supplement our well known traditional measures and even more promising new techniques and methods are already being studied (21,22). Optimistically some will sure shine bright in the future.

Conflicts of interest:
None declared.

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Antagonist

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The survival rate of patients diagnosed with cancer has greatly improved in recent decades on the basis of advances in early detection and more effective new therapeutic options. The estimated 5-year survival rate in the 70's was 50% whereas now it exceeds 64%.

Some chemotherapy drugs can be cardiotoxic inducing serious diseases that complicate the outcome. This group should include anthracyclines (doxorubicin), alkylating agents (cyclophosphamide), anti- Her-2 receptor monoclonal antibodies (Trastuzumab) and new tyrosine kinase inhibitors (Lapatinib)

This has resulted in an increasing number of pa-

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tients (an estimated 10 million in USA) exposed to chemotherapy, who are cured or with oncological disease in remission, that may develop heart failure, increasing morbidity or even causing death.

Cardiotoxicity may manifest as acute myopericarditis, arrhythmia and left ventricular dysfunction during treatment administration. This circumstance is rare and usually regresses with drug discontinuation. Subacute manifestations of cardiotoxicity occur within one year after treatment completion, whereas long-term manifestations appear more than one year after ending treatment and have the greatest incidence and worst prognosis. (1)

Early identification of patients at risk of developing cardiotoxicity when still in the subclinical stage has led to the development of recommendations for cardiac function monitoring during and post chemotherapy treatment (2, 3), mostly based on the determination of LVEF by echocardiography or nuclear medicine.

Left ventricular ejection fraction by echocardiography is usually obtained with the biplane Simpson method, a non-invasive and safe procedure as the patient is not exposed to radiation. The method has its limitations; upon which I will not enter into details as I am sure my colleague will do so in his agonist position. Some of these limitations are: calculations based on presumed LV geometry, preload and afterload sensitivity, and the need for an adequate echocardiographic window for optimal visualization of endocardial borders, which can be improved with the use of contrast and intra- and interobserver variability.

As three-dimensional ultrasound echography allows acquisition of ventricular volumes and LVEF without a geometric presumption, it is the method whose values best correlates with the gold standard of NMR.

Chemotherapy-induced cardiomyopathy is defined as functional impairment, generally global or sometimes more marked in the septum, which leads to a reduction of LVEF of > 5% to < 55% with symptoms of heart failure or an asymptomatic reduction of LVEF of > 10% to <55%. (4)

The analysis of 4 clinical trials involving more than 13000 breast cancer patients receiving adjuvant treatment with trastuzumab and using LVEF to assess toxicity may be used as a parameter of its usefulness in clinical practice.

In the HERA trial, which included 5102 patients, the incidence of symptomatic heart failure was 2.15% in the trastuzumab arm compared with 0.12% in the control group. In this study, heart failure presented class III/IV functional capacity in 0.6% of patients treated with trastuzumab. A significant decrease in LVEF was observed in 3.0 % of patients in the trastuzumab arm compared to 0.5 % of patients in the observation arm, (5) with one cardiac-related death reported in the control group. Most patients with cardiac dysfunction had symptomatic improvement and LVEF recovery within 6 months of trastuzumab discontinuation and initiation of treatment with ACE inhibitors and B-blockers.

The NSABP B-31 study for cardiac events reported an incidence of the composite endpoint of HF FC III/IV or cardiac death of 4.1% in the trastuzumab group (all were HF cases) vs. 0.8% in the control group, where one death for cardiac causes was reported. In almost all patients symptomatic and LVEF improvement was seen at 6-month follow-up. Trastuzumab was discontinued in 19% of patients, in most cases (14.1%) due to a significant and asymptomatic LVEF drop. (6)

The NCCTG N9831 study revealed an incidence of the composite end point of HF FC III/IV or cardiac death of 2.9% in the trastuzumab group with one death attributable to cardiac causes in each group.

In the BCIRG 006 study, there was 0.8% incidence of HF FC III/IV. The percentage of patients experiencing a significant drop in asymptomatic LVEF was 8.6%, 10% and 18% in each of the three treatment arms. There were no cardiac deaths after a 3-year follow-up.

ALTERNATIVES TO EJECTION FRACTION

With the aim of improving cardiotoxicity detection during the subclinical stage, several studies have been conducted using different methods, validated in other pathologies, that are compared and proposed as LVEF surrogates.

Strain allows quantification of the degree of myocardial deformation during systole and is expressed as percent deformation relative to the original length. It can be expressed in two forms: Strain as percent deformation (%) and strain rate as deformation velocity (1/s). (7) These measurements may quantitatively assess segmental contractility. They were initially described as derived from tissue Doppler and subsequently from two dimensional echocardiography or speckle-tracking

The acquisition of strain and strain rate by two-dimensional method has also the limitation of a good ultrasonic window for adequate imaging. In a study of 105 healthy patients, 7% were excluded as a result of poor image quality, i.e. it had a feasibility of 93% and although the calculation was performed by a semi-automatic method, the intra and interobserver variability was surprisingly high (circumferential strain 13%, 42% and 15. 5%; longitudinal strain 15%, 96% and 15.79%; circumferential strain rate 14%, 78% and 13.47%, and longitudinal strain rate 17%, 9% and 15.02%). (8)

Two-dimensional strain has more advantages than Doppler-derived strain as it takes less time to calculate and is less affected by ultrasound angle. Consequently, it has become a powerful tool to calculate regional systolic function and has even surpassed LVEF in predicting mortality in the general population. (9) Therefore, it is not the method what is criticized here, but its clinical utility in this type of population.

In a multicenter study involving 43 breast cancer patients treated with anthracyclines and trastuzumab, echocardiographic parameters and dosage of Troponin I and BNP were evaluated at baseline and at 3 and 6 months after treatment initiation. Nine patients developed cardiotoxicity, 1 patient at 3 months and 8 patients at 6 months. (10). Left ventricular ejection fraction at baseline and at 3 months showed no significant changes, thus failing to detect early cardiotoxicity. At 3 months, peak longitudinal strain decreased more than 10% in 14 patients with 78% sensitivity, 79% specificity and 50% PPV to detect toxicity at 6 months, i.e., only half of the patients with changed values identified by the method developed subsequent toxicity.

Something similar happened in 12 patients with troponin I elevated values, with 67% sensitivity, 82% specificity and 50% PPV to detect toxicity at 6 months.

A combination of both methods revealed 55% sensitivity, 97% specificity and 83% PPV to detect toxicity at 6 months. i.e., it was able to identify half of the patients who suffered toxicity.

In a cross-sectional study, 70 asymptomatic women who had received anthracycline chemotherapy, with the addition of trastuzumab in 27% of cases, for a mean of 50 months prior to enrollment, were compared with a control group of 50 healthy women. (11) Left ventricular ejection fraction was not significantly different between both groups: (60.4% ± 3.1%) in the treatment group vs. (61.7% ± 3.9%) in the control group. Conversely, global longitudinal strain, obtained with the speckle tracking method, was significantly lower in the treatment group (-18.1% ± 2.2%) vs. (-19.6% ± 1.8%) in the control group with p = 0.0001, and in 26% of cases strain was lower than the lowest value obtained in the control group. Radial strain showed no difference between both groups.

These alterations in systolic function detected by 2D strain had no clinical translation since all patients were asymptomatic after nearly 6 years of treatment completion, with normal ventricular dimensions and a more than acceptable LVEF. Intra and interobserver variability was 3.7% and 4.8% respectively.

A similar finding was observed in a cross-sectional study that compared 45 children treated with anthracyclines vs. a control group. All patients had completed treatment more than a year before, had no signs of cardiac dysfunction and were asymptomatic with a shortening fraction within normal range. However they revealed a significant reduction in longitudinal strain (-17.6% ± 3.0% vs 19.0% ± 2.2%, p = 0.012) and radial strain (40.1% ± 15.6% vs. 50% ± 16.4%, p = 0.006) compared to the control group. (12)

T Sai et al. studied ventricular function comparing 47 lymphoma survivor patients who had completed treatment 20 years before inclusion in the study against a control group of 20 healthy patients. Twenty-seven patients had been treated with radiotherapy plus doxorubicin (Group 1) and 20 patients had been treated with radiation therapy alone or in combination with non-anthracycline drugs (Group 2). Two-dimensional longitudinal strain showed significantly lower values in patients treated with anthracyclines compared with Group 2 (-16.1% ± 1.9% vs. 17.5% ± 1.7%, p <0.05) and with healthy controls (-20.4% ± 1.7%, p < 0001). Two-dimensional LVEF showed similar values in both groups (55% ± 8% vs. 56% ± 6%, p = 1) which were, however, significantly lower than those obtained in healthy patients (62% ± 5%, p <0.05). (13)

Hare et al. prospectively evaluated ventricular function in 35 patients with breast cancer who were treated with anthracyclines and trastuzumab. (14) For that purpose 152 studies were assessed at baseline and every three months during one year follow-up. Left ventricular ejection fraction obtained by 2D and 3D, and strain and strain rate derived from Doppler and speckle tracking, were analyzed. During follow-up, 9 patients (26%) evidenced decreased LVEF estimated by 2D and 4 patients (11%) showed a similar decrease in the 3D analysis. In all cases except one, LVEF remained over 50%. In 18 patients (51%) a decrease > 1 SD (standard deviation) in the longitudinal strain was reported and 13 patients (37%) had a similar fall in the radial strain obtained by 2D, three of which showed a drop in LVEF> 10%. In the analysis of 14 patients with impaired longitudinal strain whose follow-up was extended to 22 ± 6 months, 2 cases (14%) had a drop in LVEF >10%.

What was the clinical translation? Only 2 patients had to discontinue treatment because of symptoms consistent with cardiac dysfunction. In the first case, in addition to the alteration in longitudinal and radial strain, a LVEF drop of 11 points (from 66% to 55%) was reported. In the second case the LVEF fell from 60% to 45%.

Once more, how do we move from 51% abnormal patients determined by longitudinal strain to 5% who had clinical involvement?

In a pilot study, which included 16 elderly patients with breast cancer, who had received treatment with liposomal doxorubicin, the authors observed a significant reduction in Doppler-derived longitudinal and radial strain and strain rate. However, no significant difference in LVEF after 6 cycles of treatment was found, and none of the patients showed signs of heart failure during follow-up. (15)

The administration of therapeutic doses of doxorubicin was associated with myocyte degenerative changes obtained by biopsy in 27 out of 29 patients studied. (16)

Ewer et al. found that in 173 electron microscopy biopsies of patients treated with adriamycin, only 16 did not show any degree of alteration. Alterations in the biopsy correlated with the cumulative dose of anthracyclines, whereas there was no relationship with LVEF estimated by echocardiography or nuclear medicine. (17)

According to the endomyocardial biopsy study we should accept that all patients exposed to these drugs have cardiac involvement, as even at doses as low as 45mg/m2 biopsies have detected ventricular mass reduction and reduced nucleotides, implying that there is no dose lacking cardiotoxicity. (18, 19) This alteration triggers compensatory mechanisms and for some reason not yet fully understood some patients deplete their contractile reserve and myocardial damage becomes clinically evident.

If we had a sufficiently sensitive noninvasive method we should be able to detect cardiac involvement in all patients treated.

Methods that assess myocardial deformation such as strain and strain rate show some of this, revealing contractile dysfunction which, as it may not overcome the compensatory mechanisms, is still not detected by a drop in LVEF. The point is that because this contractile dysfunction was seen only in some patients, it has become clinically relevant.

CONCLUDING REMARKS

The cardiologist responsible for the evaluation and monitoring of patients treated with potentially cardiotoxic drugs has among his functions the unrewarding task of suggesting the oncologist to discontinue treatment, perhaps implying a turning point in the possibilities of prognosis and survival.

According to current recommendations this decision is based on the decrease in LVEF with the results already described.

Let us now presume that by mid-treatment, the patient presents with a significant drop in the global longitudinal strain is his scheduled assessment. What conduct should the cardiologist adopt?

Without a clear cut-off point and a specificity as low as 50%, how to differentiate whether the patient will develop significant cardiotoxicity that justifies leaving him without the benefit of treatment, or whether he will be one of the patients who after several years of treatment completion have altered strain but are asymptomatic and with normal LVEF?

Therefore, I think that strain may be a more sensitive and a better indicator of long-term prognosis in the general population, but leaves the crucial point of treatment discontinuation indication unanswered.

It is not yet time to replace LVEF at this point and future clinical work may find the appropriate cutoff point to answer this question.

Perhaps the early prescription of ACE inhibitors and B blockers in the population with altered strain may result beneficial and should be tested in future clinical trials.

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AGONIST'S REPLY

In current practice there is closer collaboration between cardiologists and oncologists. This collaboration has now been adopted as the new field of "cardio-oncology". With advancement in imaging technology, newer imaging technology which allows earlier detection of cardiac mechanical systolic dysfunction has emerged as the new tool for detection of chemotherapy induced cardiomyopathy. This new imaging technique (strain analysis) has been cited in several main medical journals and has been well received by both specialties.

During chemotherapy, subclinical changes, which are not sufficient enough to cause a drop in left ventricular ejection fraction are common. The patients are more educated about all the pharmacologic possibilities and some even come prepared to quote available literature. In our center, discussion of treatment options in susceptible patients occurs following close collaboration between the oncologist, cardiologist and the patient.

If cardio-toxicity is detected these options may include: dose interval modifications; treatment vacations; and in the case of doxorubicin, the addition of dexrazoxane or the use of slow infusion regimens. The concomitant use of anti-remodeling agents is another reasonable alternative in selected cases. These are, however, more timely in cases where we have preclinical information that leads to the suspicion of a change in cardiac function.

In cases of using the LVEF as "guide" we are then technically dealing with a process of "unknown duration". In some cases it may be irreversible. The opportunity to see an event before it would leave measurable dysfunction should be considered precious. It opens the door to opportunities that perhaps do not exist otherwise.

The reality is that there is an ongoing revolution in the care of the cancer patient. Not only there is an unprecedented amount of anti-cancer agents in different stages of drug approval in the US, but there is a true push for real individualized care, largely genetic- mutation based. Changes in pharmaco-oncology are dynamic and real. It is one of the many reasons that cardiologists will need to increase collaboration and improve the depth of cardiac function evaluation, using the most precise methods. Methods that are superior in dependency from physiologic variables and predictive power.

Dr. Jose Banchs

ANTAGONIST'S REPLY

I agree with Dr Banchs that there is an early strain involvement which precedes ejection fraction alteration, so it seems sensible to implement a therapy with enalapril and B blockers even though this is not yet proven by any clinical trial.

In this sense, based upon information provided by myocardial biopsy studies that show structural damage even in those receiving low doses of anthracyclines, it should be useful to ask if this treatment should not be recommended to all patients receiving cardiotoxic drug therapy or at least to all patients that may tolerate it. In this way we would even go a step further. This strategy could be evaluated simply and economically in large randomized controlled trials, to rule out any interference with the central strategy which is cancer treatment.

In the available studies commented here, patients with altered strain have 9 times greater possibility of developing heart failure than those with non-reported strain alteration.

However this altered strain does not always predict the onset of cardiac failure, but only the probability of suffering it, which in the worst case is 50% (PPV 50%), while the other 50%, although presenting altered myocardial deformation detected by strain, overcome the insult and maintain a good pump performance. This is not a minor fact when deciding treatment discontinuation.

Therefore, in this scenario and in the light of current evidence, it is my opinion that ejection fraction should remain in force and should not be replaced by these new techniques to which I would assign an additional role to enhance our ability to perform an early diagnosis.

Dr. Natalio A. Gastaldello