Cardiotoxicity: Left Ventricular Dysfunction

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8.1 Which Drugs Are Involved

The left ventricular dysfunction (LVD), from asymptomatic reduction of left ventricular ejection fraction (LVEF) up to heart failure (HF), is probably the most studied and feared late effect of anticancer therapy because it is often unpredictable and because it has a poor prognosis. It may result from many anticancer drugs through different mechanisms and often for a different combination of cardiotoxic effects in a polychemotherapy schedule.

8.1.1 Definition and Graduation of LVD

Historically, the LVD from chemotherapy was considered like a synonym of "cardiotoxicity." In literature, there are many definitions and classifications of LVD, but actually, in an expert consensus document, the American Society of Cardiology with the European Association of Cardiovascular Imaging defined LVD as a significant decline of left ventricular performance (from baseline or before anticancer therapy), measured by an LVEF reduction up to 10 % points with a final LVEF value <53% [1] independently in the presence or not of heart failure symptoms, with a significant reduction of the global longitudinal strain (GLS) index, measured by 2D echo, up to −19 %. This society believes that the value of cardiac troponin I (TnI) is also important to detect the asymptomatic or preclinical LVD, because the high level of TnI reflects the loss of myocardial cells due to drug toxicity.

This last definition seems to be useful because it identifies the LVD not for only one aspect and by a single parameter (LVEF) but by a series of different parameters (biological, LV contractility, kinetics).

Therefore, it is crucial to detect periodically the left ventricular performance or LVEF with echocardiography or, less frequently, with cardiac magnetic resonance (CMR) or MUGA scan (see the next chapter), before, during, and after anticancer therapy administration, maybe for all life. But it is evident that, actually, it's not possible to define LVD only with the LVEF value.

However, the graduation of severity of cardiotoxicity is often based on LVEF. The Common Toxicity Criteria Manual (National Cancer Institute—Cancer Therapy Evaluation Program) version 2.0 (1999) is probably the most simple and balanced classification available (see Table 8.1). This classification does not consider the GLS or TnI value, but it is quite useful to identify the severity of cardiotoxicity.

Table 8.1 Grading of LVD

Grade I	Asymptomatic decline in LVEF of >10 % from baseline evaluation
Grade II	Asymptomatic decrease in LVEF of <50 % or ≥20 % compared with baseline value
Grade III	Heart failure responsive to treatment
Grade IV	Severe or refractory heart failure or requiring intensive medical therapy and/or intubation
Grade V	Death related to cardiac toxicity

LVEF left ventricular ejection fraction
Adapted from National Cancer Institute Common Terminology Criteria for Adverse Events 2.0 (1999)

Unfortunately, there is no uniformity of opinion to identify the cardiotoxicity and to define this condition; they do not have permission to do a systematic review or meta-analysis of cardiotoxicity, to learn more about those aspects that are actually still unclear [2].

8.1.2 Anthracycline-Related LVD

The anthracyclines, commonly used to treat many hematologic and solid malignances such as Hodgkin's and non-Hodgkin's lymphomas and breast and gastric cancer, are the most studied and most frequent drugs with established LVD.

In 2005, Lipshultz [3] defined and classified the anthracycline-related LVD in three types depending on the time of appearance:

- **Acute cardiotoxicity:** during chemotherapy administration, usually reversible, and characterized by transient contractile LV depression (low incidence)
- **Early-onset chronic progressive cardiotoxicity:** within 1 year after the end of chemotherapy, dose dependent, not reversible spontaneously, and associated by a poor prognosis
- **Late-onset chronic progressive cardiotoxicity:** more than 1 year after the end of chemotherapy

More recent findings, however, suggest that anthracycline-related cardiotoxicity is most likely a unique and continuous phenomenon that starts with myocardial cell injury and is followed by progressive LVEF decline that, if disregarded and not treated, progressively leads to overt HF [5].

This significant late effect seems to have several mechanisms, but free radical formation and topoisomerase 2B-related DNA damage, are generally accepted as the main mechanisms [6–8].

There are several risk factors that increment the probability of anthracycline-related LVD (summarized in Table 8.2): firstly, cumulative dose of drugs. In fact, the prevalence of cardiomyopathy increases significantly when patients are given doses of doxorubicin ≥550 mg/m^2 (7% risk of symptomatic HF; 26% of symptomatic HF in elderly patients) [4, 9, 10]. Age, cardiac risk factors (e.g., hypertension, diabetes, smoke), concomitant radiotherapy, the type of anthracycline, female gender, and other conditions appear to increase (or decrease) the risk of LVD.

Actually the real incidence of chemotherapy-related cardiotoxicity is unclear, because we have several evidences stating that the incidence of cardiovascular diseases, especially heart failure in elderly patients, increased in cancer survivors, during the follow-up [11, 12].

The liposomal formulations of doxorubicin, usable only in selected conditions, have proven to be less cardiotoxic of the traditional molecule [13].

8.1.3 Non-anthracycline-Related LVD

Anthracyclines are not the only chemotherapy drugs related to LVD. Antimicrotubule and alkylating agents seem to increase the anthracycline-related LVD risk in a concomitant polychemotherapy [14]. The cardiovascular risk in patients treated with other conventional chemotherapy drugs is negligible.

Table 8.2 Risk factors for anthracycline cardiotoxicity

Risk factor	Aspect
Cumulative anthracycline dose	Cumulative doses >500 mg/m^2 associated with significantly elevated long-term risk
Rate of anthracycline administration	Prolonged administration to minimize circulating dose volume may decrease toxicity; results are mixed
Individual anthracycline dose	Higher individual anthracycline doses are associated with increased late cardiotoxicity, even when cumulative doses are limited
Type of anthracycline	Liposomal encapsulated preparations may reduce cardiotoxicity. Conflicting data exist about anthracycline analogues and cardiotoxicity differences
Radiation therapy	Cumulative radiation dose >30 Gy; prior or concomitant anthracycline treatment
Concomitant therapy	Trastuzumab, cyclophosphamide, bleomycin, vincristine, amsacrine, and mitoxantrone may increase susceptibility/toxicity. Others are implicated as well
Preexisting cardiac risk factors	Hypertension; ischemic, myocardial, and valvular heart disease; prior cardiotoxic treatment
Comorbidities	Diabetes, obesity, renal dysfunction, pulmonary disease, endocrinopathies, electrolyte and metabolic abnormalities, sepsis, infection, pregnancy
Age	Both young and advanced age at treatment are associated with elevated risk
Sex	Females are at greater risk than males

Partially modified by Lipshultz, Heart 2008 [4]

8.1.4 Targeted Therapy and LVD

Not only chemotherapy can cause LVD but also the new anticancer molecular targeting drugs such as monoclonal antibody-based tyrosine kinase inhibitors (TKI), trastuzumab or bevacizumab, and new TKI small cell sunitinib or sorafenib, from asymptomatic LVEF decrease to a symptomatic heart failure, but different pathophysiological mechanisms are involved.

Trastuzumab

Trastuzumab is a monoclonal antibody directed toward some epidermal growth factor receptors (*HerB2*) overexpressed in about 30 % of breast cancer and increase significantly the efficacy of chemotherapy in HerB2+ patients treated in a metastatic and in adjuvant setting [15, 16]. This efficacy depends on the block of intracellular EGFR signal that induces apoptosis by increasing intracellular calcium level. But the link with the HerB2 receptors present in the surface of cardiomyocytes causes also loss of these cells.

The trastuzumab-related LVD depends on the expression of HerB2 that may be transiently upregulated by a compensatory mechanism following cardiac stress in a myocar-

Table 8.3 Classification of LVD

	TYPE I (myocardial damage)	Type II (myocardial dysfunction)
Characteristic agent	Doxorubicin	Trastuzumab
Clinical course, response to CRCD therapy	May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress	High likelihood of recovery (to or near baseline cardiac status) in 2–4 months (reversible)
Dose effects	Cumulative, dose related	Not dose related
Mechanism	Free radical formation, oxidative stress/damage	Blocked ErbB2 signaling
Ultrastructure	Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)	No apparent ultra structural abnormalities
Noninvasive cardiac testing	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion	Decreased ejection fraction by ultrasound or nuclear determination: global decrease in wall motion
Effect of rechallenge	High probability of recurrent dysfunction that is progressive, may result in intractable heart failure and death	Increasing evidence for the relative safety of rechallenge; additional data needed
Effect of late sequential stress	High likelihood of sequential stress-related cardiac dysfunction	Low likelihood of sequential stress-related cardiac dysfunction

CRCD chemotherapy-related cardiac dysfunction
From Ewer, JCO 2005 [18]

dial cell [17]. For this reasons, it is not prudent to administer trastuzumab concurrently with anthracycline but few weeks after the end of this chemotherapy.

In 2005, Ewer called "type 1" the LVD caused by anthracycline or other chemotherapy, and "type 2" the LVD caused by targeted therapy, after highlighting that a group of HF trastuzumab-related patients with breast cancer would recover LVEF as a result of HF therapy and discontinuation of trastuzumab [18, 19]. Many differences are reported from these two conditions: relationship of cumulative dose, presence of histological abnormalities, and prognosis. Table 8.3 summarizes these differences.

Bevacizumab and TKI Small Cell

Bevacizumab is a monoclonal antibody currently used in gastrointestinal cancer patients. In the literature, HF incidence in bevacizumab-treated patients are reported to be from 1 to 3% [6]. The mechanism of HF associated with bevacizumab may be related to uncontrolled hypertension and inhibition of vascular endothelial growth factor (VEGF)/VEGF receptor signaling that induces compensatory hypertrophy in patients with hypertensive and ischemic disease. The HF that results is a hypertensive failure, so we must carefully

control the hypertensive patients. Cardiotoxicity in patients treated with bevacizumab is potentially reversible with discontinuation of drug administration, like the other "type 2" dysfunctions.

Sunitinib and sorafenib are two TKI small cell used in advanced renal cell carcinoma and hepatic tumors. These drugs appear to share the same cardiotoxic mechanism with bevacizumab but act within the cell and not outside. Cardiac dysfunction, manifested as HF or asymptomatic declines in LVEF, has also been noted but widely underestimated in the past; the incidence of HF is estimated to be 4–8 %, while the incidence of asymptomatic LVEF decline is even higher, up to 28 % for LVEF declines ≥10 % [20, 21].

8.2 How to Monitor

Highly effective chemotherapeutic agents may cause cancer therapeutics-related left ventricular dysfunction (LVD). To monitoring of left ventricular function is very important for early detection of LVD and prompt treatment that may prevent LV remodeling and the progression to the HF syndrome.

- **Echocardiography (ECHO)** is also a precious tool for the evaluation of left ventricular function, pericardium, valves, and right chambers that all may be damaged by cancer therapy.
- **Cardiac magnetic resonance (CMR)** could be useful for improving echocardiographic information when this is unsatisfactory or when tissue characterization is needed. Contrast-enhanced CMR offers a unique capability to identify subtle myocardial abnormalities, such as diffuse fibrosis, compared with other imaging techniques [22, 23], and anthracycline-related myocardial fibrosis [24, 25]. Although this technique suggests promise for future diagnosis and possibly prediction of risk for cardiomyopathies, its current use is limited to research studies.
- **Radionuclide angiography (MUGA)** has been referred as the "gold standard" to monitor anthracycline-related damage due to its high accuracy and reproducibility of LVEF measurements [26–27], but it has the main disadvantage in radiation exposure. Thus, it is frequently used as an adjunct and a complementary technique to echocardiography.

The ECHO represents the imaging modality of choice for evaluation and monitoring of LVD.

8.2.1 LV Systolic Function

The most commonly used parameter for monitoring LV function with echocardiography is ejection fraction (LVEF). In cancer patients, changes in LVEF indicative of LV damage can be more appropriately identified comparing baseline and follow-up studies.

Accurate calculation of LVEF should be done with the best method available in a given echocardiography lab. Consistency with regard to the method used to determine LVEF should be maintained whenever possible during treatment and surveillance after treatment. Importantly, the digital images obtained to calculate LVEF on follow-up echocardiography should be visually compared with the previous ones to minimize reader variability.

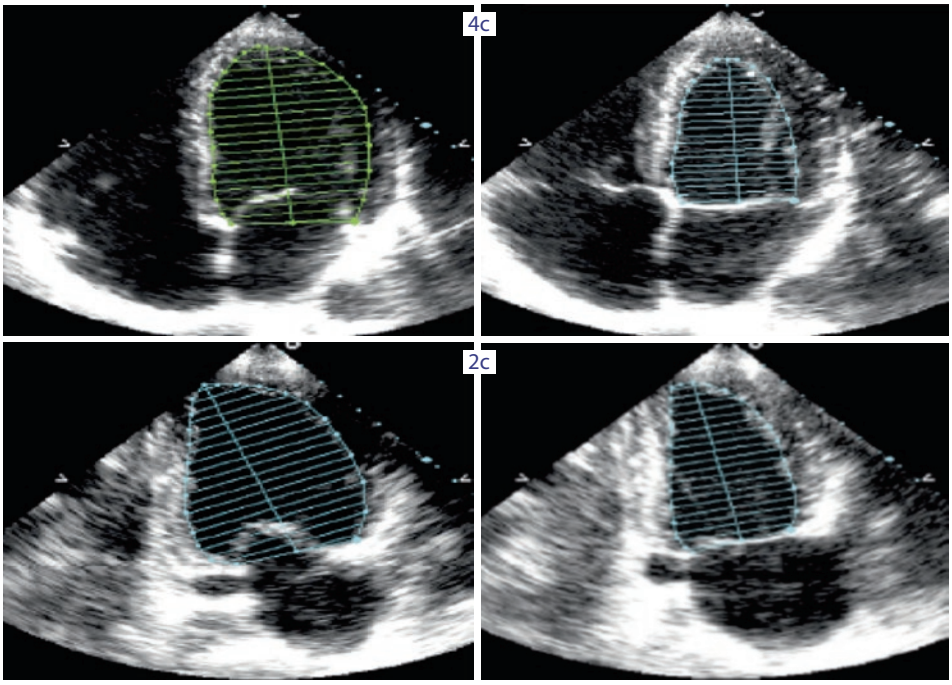

Fig. 8.1 LVEF using biplane Simpson's method

According to joint recommendations from the American Society of Echocardiography (ASE), and the European Association of Echocardiography (EAE) [28], the methods of choice for LV volumes quantitation and LVEF calculation are:

- The modified biplane Simpson's technique (method of disks) by 2DE (Fig. 8.1).
- The use of an automated or semiautomated method for identifying LV endocardium, compared with manual tracing of endocardial contour required by 2D method, provides a more accurate estimation of LV volumes (Fig. 8.2).
- A contrast agent should be used when two contiguous LV segments from an apical view are not seen on non-contrast images.
- 3D evaluation of LVEF is recommended because it is more accurate than 2D modality for LV volume measurement with a precision, which is comparable to that of CMR.
- Advantages: better accuracy in detecting LVEF below the lower limit of normal, better reproducibility, and lower temporal variability than 2DE in patients with cancer treated with chemotherapy.
- Limits: costs, availability, high-quality images, training, and expertise of operators for a clinical application limit the wide application of 3DE in the oncological setting.

A LVEF (assessed by 2D modified Simpson's rule) >52 % for men and >54 % for women is suggestive of normal systolic function [29].

As indicated in previous chapter, consensus of ASE-EACVI [1] proposed for the diagnosis of cardiac toxicity.

- A decrease in the LVEF of >10 % points, to a value <53 %. However, in a recent ESC position Paper [29] the Autors has decided to consider the lower limit of normal of

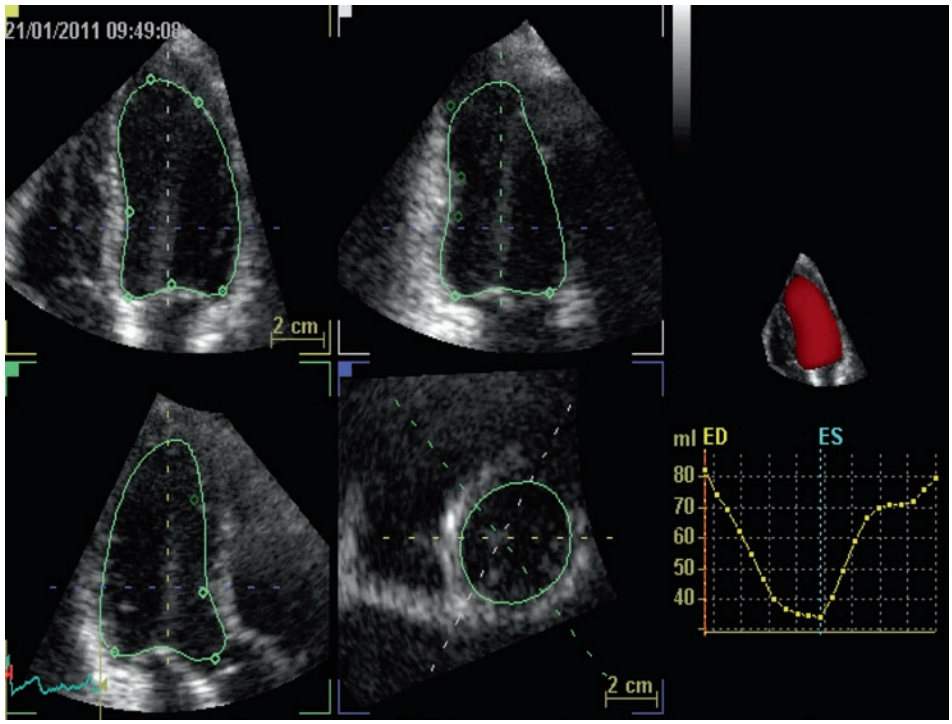

Fig. 8.2 LVEF using automated 3D method

LVEF in echocardiography also 50 %, in line with the definition of cardiotoxicity commonly used in registries and trials in patients with cancer.

- That should be confirmed by repeated cardiac imaging performed 2–3 weeks after the baseline study

The calculation of LVEF should be combined with assessment of the wall motion score index; septal and apical pattern of LV dysfunction have been more frequently found at an early stage of LVD in the presence of a quite normal LVEF; therefore, a careful analysis of regional alterations is strongly worthwhile beyond the LVEF assessment.

8.2.2 LV Diastolic Function

A comprehensive assessment of LV diastolic function should be performed in the oncology setting, although diastolic parameters have not been found to be prognostic of LVD.

According to the joint ASE-EACVI [30], evaluation of LV diastolic function include:

- Diagnosis of LV diastolic dysfunction (Fig. 8.3)
- Estimate of LV filling pressure and grading LV diastolic function (Fig. 8.4)

However, use of the E/e' ratio remains questionable in the oncological setting, as E and e' velocities fluctuation in these patients could be the consequence of changes in loading conditions as a result of side effects associated with the chemotherapy (nausea, vomiting, and diarrhea) more than the result of a real change in LV diastolic performance.

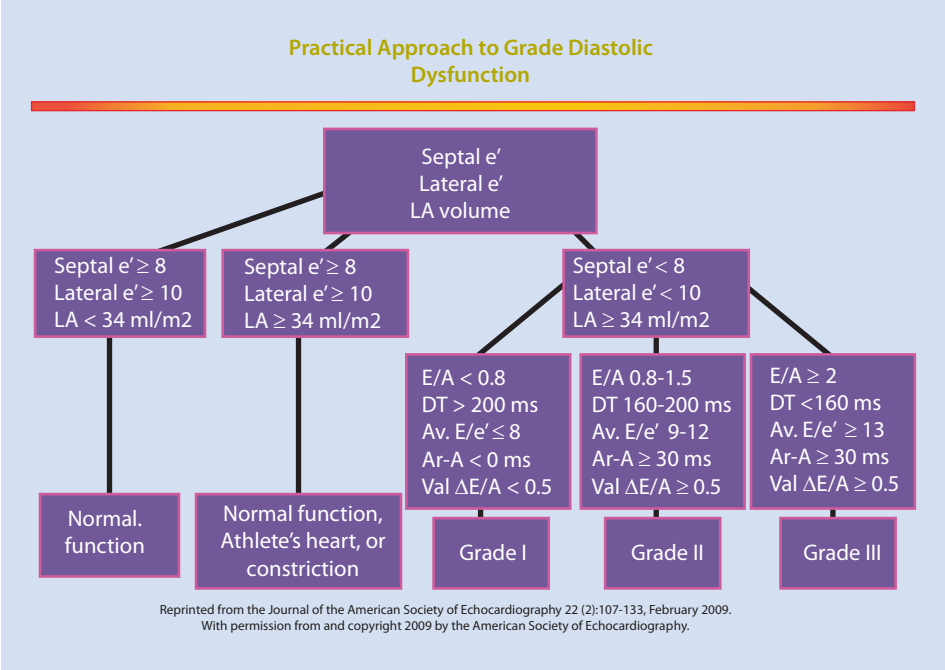

Fig. 8.3 Algorithm for diagnosis of LV diastolic dysfunction if LVEF is normal

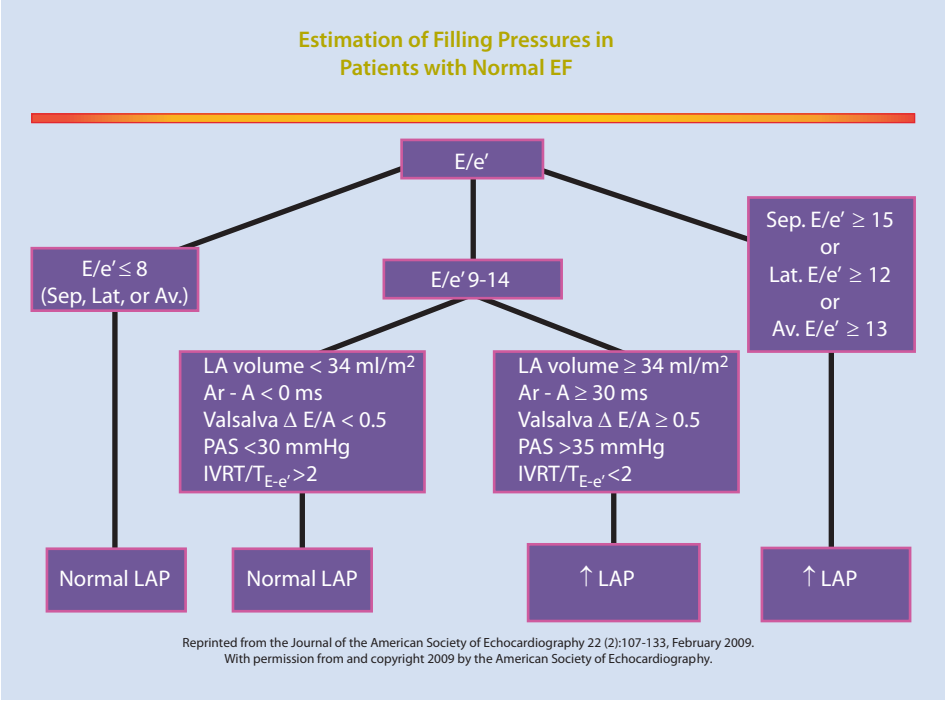

Fig. 8.4 Algorithm for estimation of LV filling pressure and grading diastolic function if LVEF is depressed

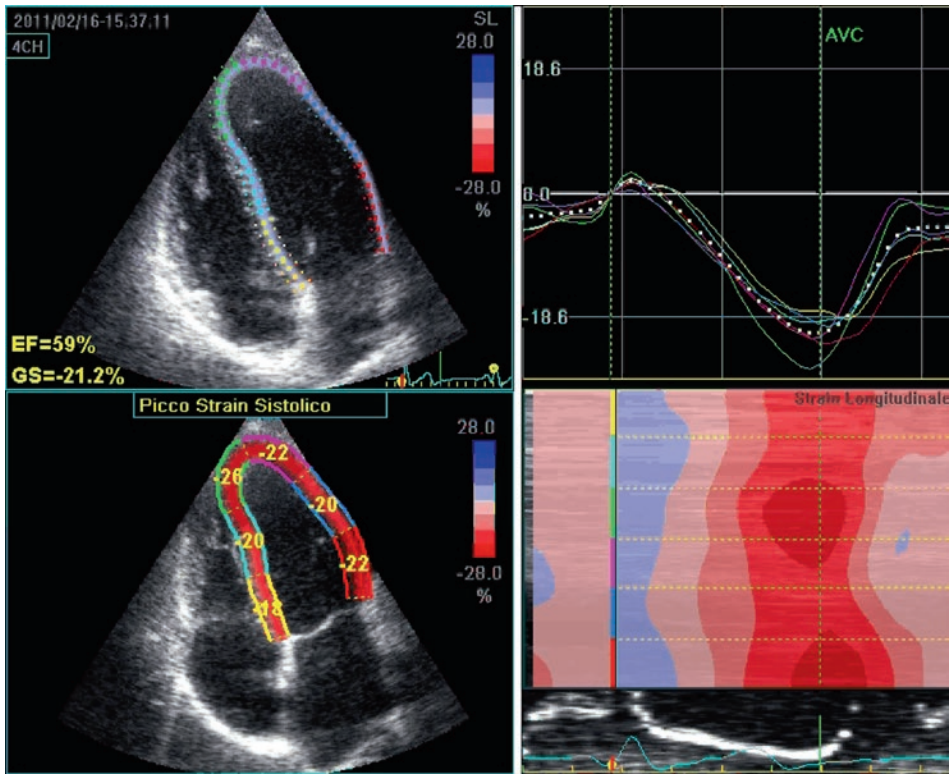

Fig. 8.5 Longitudinal strain using STE

8.2.3 Myocardial Deformation

Myocardial deformation (strain) can be measured using different ultrasound techniques: Doppler strain imaging (DSI) and 2D/3D speckle tracking echocardiography (STE).

- DSI has been the first method used. It showed to be more sensitive than LVEF assessment in recognizing LV systolic dysfunction caused by chemo- and radiotherapy, both in adults and children; was able to identify early cardiotoxicity; and could reveal differences in myocardial function at a regional level, identifying those segments that are more affected by the cardiotoxic effect (as interventricular septum) [31].
- STE allows for a frame-by-frame tracking of natural acoustic markers and it is preferred because of a lack of angle dependency and not influenced by translational movement, tethering from adjacent myocardium and signal noise.

Different deformation parameter can be evaluated. In general, the maximal extent of the systolic myocardial deformation (peak systolic strain) and its peak rate (peak systolic strain rate) have been used, both regionally and globally. In general, assessment of longitudinal strain, and specifically global longitudinal strain (GLS) using 4, 2, and 3 chambers view, has provided more consistent results than radial and circumferential myocardial deformation analysis (Figs. 8.5 and 8.6).

- GLS is the optimal parameter of deformation for the early detection of subclinical LV dysfunction.

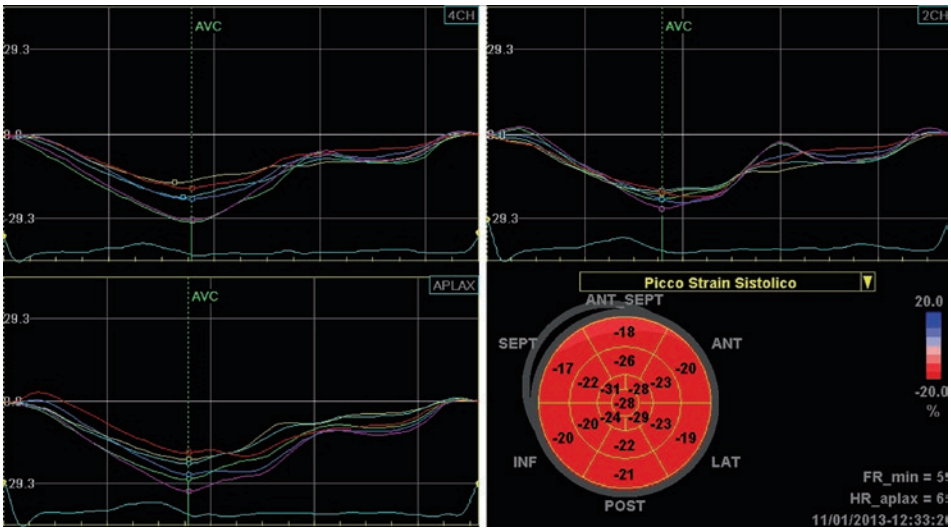

Fig. 8.6 Global longitudinal strain

- The measurements during chemotherapy should be compared with the baseline value. In patients with available baseline strain measurements (Fig. 8.7).
  - a relative percentage reduction of GLS of <8 % from baseline appears not to be meaningful.
  - A relative percentage reduction of GLS of >15 % from baseline are very likely to be abnormal.

When applying STE for the longitudinal follow-up of patients with cancer, the same vendor-specific ultrasound machine and range for sex and age should be used [32] (Table 8.4).

This is important also to detect the reversibility of the myocardial damage.

8.2.4 Use of Biomarkers

Several studies admit the utility of troponins as a robust diagnostic tool for the early identification, assessment, and monitoring of cardiotoxicity [33, 34].

Troponin I (TnI) is a sensitive and specific marker for myocardial injury in adults treated with anthracycline chemotherapy and an elevation of troponin identifies patients at risk for the subsequent development of LVD.

The ASE-EACVI Consensus proposed an integrated approach for baseline assessment and monitoring of LVD [1].

- Baseline assessment (LVEF, GLS, TnI) in patients at high risk for development of LVD.
  - With established risk factors for cardiovascular disease
  - With LV dysfunction
  - >65 years of age
  - Patients scheduled to receive high doses of type I agents (>350 mg/m^2) or combination chemotherapy with both type I and type II agents

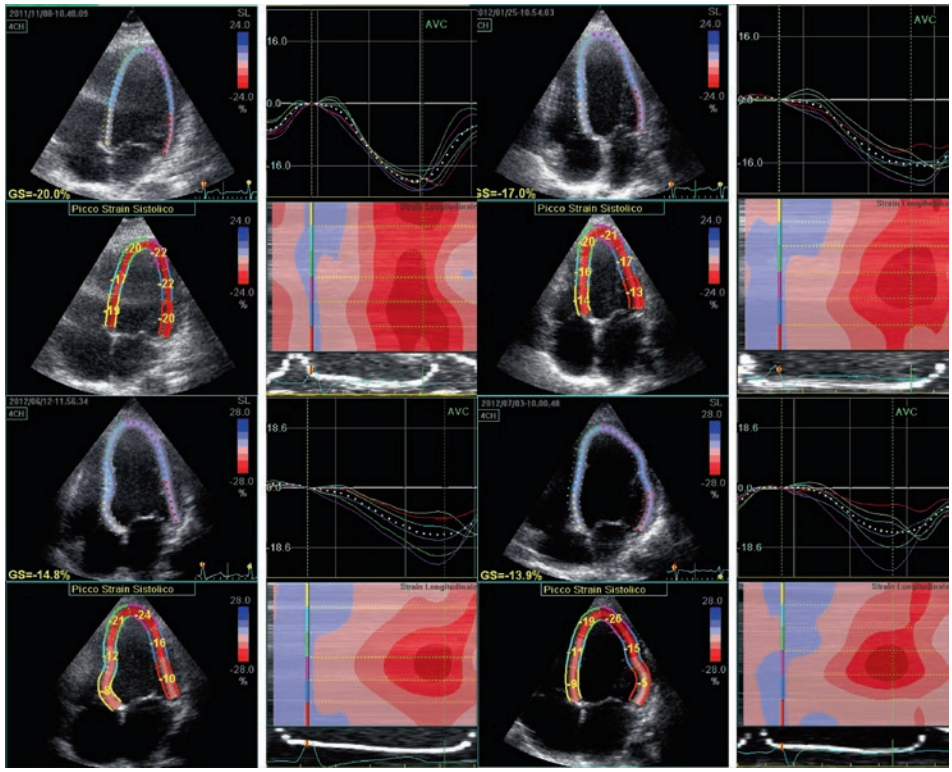

Fig. 8.7 Changes of GLS in a patient with breast cancer treated with anthracyclines (follow-up of 8 months)

Table 8.4 Reference values of global longitudinal strain for vendor, age, and gender

Vendor	Age group (y)					
	0–19	20–29	30–39	40–49	50–59	≥60
Vivid 7 or Vivid E9 (GE Healthcare)						
Male	−21.7 ± 3.1	−20.9 ± 1.9	−20.6 ± 1.9	−20.9 ± 1.8	−21.0 ± 1.9	−19.7 ± 1.4
Female	−22.4 ± 1.6	−22.3 ± 1.6	−22.8 ± 1.8	−22.6 ± 2.1	−23.3 ± 1.9	−20.9 ± 2.1
iE33 (Philips Medical Systems)						
Male	−19.4 ± 2.7	−18.8 ± 2.0	−19.1 ± 2.3	−17.9 ± 2.8	−16.9 ± 2.3	−15.8 ± 1.4
Female	−20.5 ± 2.2	−20.6 ± 2.3	−20.2 ± 2.0	−19.3 ± 0.9	−20.4 ± 1.5	−17.3 ± 2.3
Artida or Aplio (Toshiba Medical Systems)						
Male	−21.6 ± 2.0	−20.2 ± 2.0	−20.4 ± 2.2	−19.8 ± 2.3	−18.7 ± 2.6	−16.3 ± 3.1
Female	−21.2 ± 1.5	−20.2 ± 2.4	−20.4 ± 2.8	−18.7 ± 1.8	−18.3 ± 2.8	−18.6 ± 2.3

Modified from Takigiku, Circ J 2012 [32]

- If the LVEF is <53 %.
- GLS is below the limit of normal.
- Elevated TnI should be considered discussion between the cardiologist and oncologist of the risk/benefit ratio.

1. **If LVEF, GLS, and TnI are normal**, echocardiographic follow-up is recommended on the basis of the specific type of anticancer agent received.
   a. **For type I agents:** at the completion of therapy and 6 months later for doses of anthracycline <240 mg/m [2] or its equivalent. Once this dose is exceeded, measurements of LVEF, GLS, and troponin are recommended before each additional 50 mg/m [2].
   b. **For type II agents:** every 3 months during therapy for trastuzumab and at 1 month and every 3 months while on therapy with other tyrosine kinase inhibitors.
2. **The detection of subclinical LVD** is to compare the measurements of GLS obtained during chemotherapy with the one obtained at baseline.
   a. A relative percentage reduction GLS of >15 % is very likely to be abnormal,
   b. A change of <8 % appears not to be of clinical significance.
   c. The abnormal GLS value should be confirmed by a repeat study performed 2–3 weeks after the initial abnormal study.

8.3 How to Treat

Treatment of cardiac dysfunction resulting from anticancer therapy commonly follows the cardiology guideline recommendations for heart failure (HF). This practice, however, is mainly based on extrapolation from other clinical settings rather than on evidence specifically addressing HF in the cancer population.

8.3.1 Left Ventricular Dysfunction Induced by Anthracyclines

Anthracycline-induced cardiac dysfunction (ACD) is believed to be refractory to conventional therapy and to be associated with an especially poor prognosis, with a 2-year mortality rate of up to 60 % [35].

This opinion, however, is based on findings reported in old studies in which standard therapy included only the use of digoxin and diuretics [36–38], and on studies including very small populations (Table 8.5), patients with ACD has never been fully investigated because, typically, these patients have been excluded from large randomized trials.

Moreover, data on long-term outcomes of treated and untreated patients with ACD are limited. As a consequence, evidence-based recommendations for the management of cancer patients with asymptomatic and symptomatic ACD are still lacking and no definite guidelines are currently adopted.

The effectiveness of angiotensin-converting enzyme inhibitors (ACEI) and beta-blockers was prospectively assessed only in two studies involving large populations [48]. Evidence coming from these two studies can be outlined as follows:

- Initiation of ACEI and beta-blocker medications promptly after the detection of ACD is a crucial variable for recovery of cardiac function, as a strong inverse relationship

Table 8.5 Clinical studies evaluating heart failure therapy in anthracycline-induced cardiomyopathy

Treatment	Author (year)	Pts (*n*)	Mean age (yrs)	Study	FU (months)	B-LVEF (%)	F-LVEF (%)	Reported event
Dig + Diur	Lefrak (1973) [36]	2	NA	CR	NA	NA	NA	CD
Dig + Diur	Cohen (1982) [37]	1	38	CR	8	23	64	Relief of symptoms
Dig + Diur	Haq (1985) [38]	43	55	R	2–52	NA	NA	Relief of symptoms, HF, CD
Dig + Diur + ACEI	Saini (1987) [39]	3	49	CR	12–16	20	48	Relief of symptoms LVEF↑
Dig + Diur[a] Dig + Diur + ACEI[b]	Jensen (1996) [40]	9	58	PO	26	27	47	CD, HF
Dig + Diur + ACEI[a] BB[b]	Fazio (1998) [41]	1	35	CR	12	14	45	Relief of symptoms
BB BB + ACEI	Noori (2000) [42]	2 6	51	R	32	28	41	LVEF ↑
Dig + Diur[a] Dig + Diur + ACEI[b]	Jensen (2002) [43]	10	54	PO	30	27	41	HF
BB BB + ACEI	Mukai (2004) [44]	3 2	53	CR	27	37	53	LVEF ↑ NYHA ↓
ACEI ACEI + BB	Tallaj (2005) [45]	10 15	47	R	70	25	34	CD, TXS
ACEI + BB	Tabet (2006) [46]	1	52	CR	8	NA	30	HF
ACEI + BB	Cardinale (2010) [47]	201	53	P	12–96	38	46	LVEF ↑ up to ≥50 %
ACEI + BB	Cardinale (2015) [5]	226	50	P	4–228	40	52	LVEF ↑of 5 points + ≥50 %

AC anthracyclines, *ACEI* angiotensin-converting enzyme inhibitors, *B* baseline, *BB* beta-blockers, *CD* cardiac death, *CR* case report, *Dig* digitalis, *Diur* diuretics, *F* final, *HF* heart failure, *impr.* improvement, *LVEF* left ventricular ejection fraction, *NA* not available, *NYHA* New York Heart Association, *O* observational, *P* prospective, *R* retrospective, *TRZ* trastuzumab, *TKI* tyrosine kinase inhibitors, *TXS* cardiac transplantation

[a]First-line therapy

[b]Second-line therapy

exists between the time elapsed from the end of chemotherapy and the beginning of HF therapy for treatment of ACD, and improvement in LVEF—with a fourfold decrease in the chance of complete recovery from cardiac dysfunction for each doubling in time to HF treatment. In particular:
  - The highest chance to recover from ACD is observed in patients treated within 2 months from the end of chemotherapy.
  - No complete recovery in cardiac function is obtained in patients treated after 6 months.
- Cardiac surveillance, exclusively based on symptoms, may miss early detection and effective treatment of ACD.
- ACD recovery is associated with a reduction in cardiac events, when compared with patients who do not recover or who have partially recovered from ACD.
- A greater improvement in cardiac function is observed in patients receiving a combination of ACEI and beta-blockers.

Whether therapy with ACEI and beta-blockers should be either prolonged lifelong or discontinued after complete recovery of LVEF is unknown and needs further investigation.

8.3.2 Left Ventricular Dysfunction Induced by Trastuzumab

Treatment of trastuzumab-induced cardiac dysfunction (TICD) is a controversial issue.

Trastuzumab-related cardiotoxicity seems to have a more favorable outcome than ACD, as cardiac function improves after withdrawal of the drug in most cases [49].

However, the concept that TICD is a reversible condition remains in discussion [50, 51]. Follow-up data from large trials show that:
- In many patients treated with anthracyclines followed by trastuzumab, TICD does not recover.
- Up to two-thirds of patients continue to receive cardiac medication after complete functional recovery.
- Many patients continue to have a LVEF lower than baseline despite optimal HF therapy.

Although favorable data on long-term cardiac outcome of patients with TICD are emerging [52, 53], showing that the risk versus benefit remains in favor of trastuzumab, some uncertainties regarding early diagnosis and management of TICD still remain [49–51].

Guidelines for monitoring patients receiving adjuvant trastuzumab are periodically updated, but they are specifically focused on the continuation/withdrawal/resumption of trastuzumab therapy [51, 54–57].

No evidence-based recommendations for the treatment of patients developing TICD, particularly after the completion of trastuzumab therapy, have been formulated yet. To date, the evidence supporting the use of ACEI and beta-blockers in this setting is limited to case series, and it is not demonstrated in clinical trials (Table 8.6).

In clinical practice, the decision on whether to treat or not treat patients showing asymptomatic decreases in LVEF with trastuzumab is mainly based on the personal clinical experience of both cardiologists and oncologists.

Table 8.6 Clinical studies evaluating heart failure therapy in trastuzumab-induced cardiomyopathy

Treatment	Author (year)	Pts (*n*)	Mean age (yrs)	Study	FU (months)	B-LVEF (%)	F-LVEF (%)	Reported event
ACEI ACEI + BB	Ewer (2005) [18]	38	52	R	10	43	56	LVEF ↑
ACEI ACEI + BB	Cardinale (2010) [47]	251	50	PO	1–79	41	51	LVEF ↑ up to ≥50 %
ACEI ACEI+ BB	Takur (2014) [58]	79	52	R	n.a.	41	53	LVEF ↑

AC anthracyclines, *ACEI* angiotensin-converting enzyme inhibitors, *B* baseline, *BB* beta-blockers, *CD* cardiac death, *CR* case report, *Dig* digitalis, *Diur* diuretics, *F* final, *HF* heart failure, *impr.* improvement, *LVEF* left ventricular ejection fraction, *NA* not available, *NYHA* New York Heart Association, *O* observational, *P* prospective, *R* retrospective, *TRZ* trastuzumab, *TKI* tyrosine kinase inhibitors, *TXS* cardiac transplantation

Several algorithms have been proposed for management of TICD but their effectiveness needs to be confirmed in large, prospective trials. To date, the true effectiveness of ACEI and beta-blockers in improving LVEF and favorably impacting cardiac outcome in patients receiving trastuzumab remains unclear [47, 54–57, 59].

TICD recovery rate seems to be higher in patients treated with a combination of ACEI and beta-blockers [47, 59]. On the bases of current evidence, an approach based on the association of these two drugs should be considered in patients developing TICD.

- **Troponin.** The response of TICD to HF treatment may be predicted by assessment of troponin I, a well-recognized marker of myocardial injury in many clinical settings and in cancer patients receiving both old and new antitumor drugs [60].

The rise in troponin I during trastuzumab therapy represents an independent predictor of lack of recovery from TICD—with a threefold decrease in the chance of recovery from cardiac dysfunction, and it is associated with a higher incidence of cardiac events. Therefore, troponin I seems able to discriminate between reversible and irreversible cardiac dysfunction. This information may have relevant clinical implications for the oncologist who has to decide whether to resume trastuzumab or not and allows the cardiologist to distinguish patients with a more favorable cardiac outcome from those in whom a close cardiologic monitoring is mandatory, and prophylactic strategies, for prevention of clinical and subclinical TICD, should be planned [47].

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