ESC HEART FAILURE
ESC Heart Failure 2022; **9**: 3533–3542
Published online 27 July 2022 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14094

ORIGINAL ARTICLE

Right ventricular and atrial strain in patients with advanced melanoma undergoing immune checkpoint inhibitor therapy

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Abstract

Aims While immune checkpoint inhibitor (ICI) therapy significantly improves survival rates in advanced melanoma, ICI can evoke severe immune-related cardiovascular adverse events. Right ventricular (RV) dysfunction negatively impacts the outcomes in cardiovascular diseases and may be an early sign for overall cardiotoxicity. We aimed to assess RV function in melanoma patients undergoing ICI therapy using conventional echocardiographic and strain imaging techniques.

Methods and results We retrospectively examined 30 patients (40% women, age 59 ± 13 years) with advanced melanoma (stage III/IV) before and 4 weeks after the start of ICI therapy (follow-up at 39 ± 15 days); n = 15 of the patients received nivolumab, and n = 15 received the combination therapy nivolumab/ipilimumab. Two-dimensional echocardiography with assessment of RV longitudinal strain of the free wall (RV-LSFW) and assessment of right atrial (RA) strain from speckle tracking was performed at baseline and after the start of ICI therapy. Short-term ICI therapy caused a reduction of RV-LSFW (−25.5 ± 6.4% vs. −22.4 ± 4.3%, P = 0.002) and of RA strain during contraction phase (−10.6 ± 3.5% vs. −7.7 ± 3.1%, P = 0.001). Conventional parameters including tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), and pulmonary artery systolic pressure were not different between the two time points (TAPSE 26 ± 5 vs. 25 ± 5 mm, P = 0.125; FAC 38 ± 13% vs. 38 ± 14%, P = 0.750; and pulmonary artery systolic pressure 27 ± 10 vs. 25 ± 8 mmHg, P = 0.268).

Conclusions Analysis of RV and RA strain shows alterations even in a short-term follow-up, while changes in RV function are not visible by conventional RV parameters. Alterations in RV and RA strain could be early signs of cardiotoxicity and therefore should be assessed in patients undergoing ICI therapy.

Keywords Immune checkpoint inhibitor therapy; Right ventricular function; Cardiotoxicity; Cardio-oncology

Received: 13 April 2022; Revised: 3 June 2022; Accepted: 10 July 2022
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Introduction

Over the past 10 years, immune checkpoint inhibitor (ICI) therapy has revolutionized the therapeutic concept in advanced malignant melanoma.[1] ICI therapies typically target cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed death-1 (PD-1)/ligand-1. The CTLA-4 inhibitor ipilimumab and the PD-1 inhibitors nivolumab and pembrolizumab or combinations of these agents are applied in patients with advanced melanoma.[2–4]

Immune checkpoint inhibitor therapy has the risk of serious side effects, the so-called immune-related adverse events (irAEs).[5] irAEs often occur within the early phase of therapy (≤12 weeks of therapy in combination therapies consisting of ipilimumab and nivolumab),[6,7] which results in the need for very premature clinical follow-up visitations.[6]

They can affect every organ system. The most common irAEs are immune-related colitis, immune-related hepatitis, skin-related immune reactions, and immune-related thyroiditis and hypophysitis.[6] Cardiac immune-related complications are relatively rare but considerably life-threatening.[8] Because of an increasing use of ICI therapy, different aspects of cardiovascular irAEs have been identified ranging from myocardial infarction, ischaemic stroke, and pericardial disease to venous thrombo-embolism.[9–11] The most severe cardiac complication is immune-related myocarditis.[12] While ICI-related fulminant myocarditis was described to be relatively rare, preclinical evidence also indicates a risk for left ventricular (LV) dysfunction during ICI even in the absence of manifest myocarditis particularly with ICI therapies.[13–16]

Assessment of right ventricular (RV) function is of emerging importance in patients undergoing chemotherapies, radiotherapies, or immunotherapies.[17,18] While current expert consensus suggests the diagnosis of LV cardiotoxicity based on LV systolic assessment [reduction of 10% points in LV ejection fraction (EF) to a level $<$50% and/or $>$15% relative reduction in LV global longitudinal strain (LV-GLS)], the same consensus recommends the assessment of RV chamber sizes and function in case of possible RV involvement, without going into further details regarding necessary parameters, reference, or diagnosis values.[19,20] Previous investigations reported deterioration of RV function in cancer patients and during anticancer therapy,[18,21–23] and RV dysfunction is known to be a parameter of poor prognosis in other cardiovascular diseases. Both ventricles share similarities concerning their structure, but the right ventricle has significantly smaller mass and thinner walls.[24] Therefore, changes to the RV myocardium usually occur faster, and one could suggest a higher susceptibility to cardiotoxic alterations compared with the LV myocardium.[25] To date, there are no data on the effect of ICI therapy on right heart function. We therefore aimed to investigate the structure and function of the right ventricle and atrium in patients with advanced melanoma undergoing ICI therapy.

Methods

This retrospective investigation included 30 consecutive patients with melanoma who were examined in our cardio-oncology unit between July 2018 and July 2019 from our all-comers registry 'Essen Cardio-oncology Registry' (ECoR). Patients' data were analysed, when patients presented with advanced melanoma (Tumour stage III/IV) before a planned ICI therapy and ~4 weeks after the start of ICI therapy. Anthropometric measurements (height and weight) were assessed in all patients, and body mass index (BMI) and body surface area (BSA) were calculated accordingly. Data regarding different factors such as hypertension, atrial fibrillation, and premedication were acquired retrospectively from medical records. The ECoR study was approved by the institutional ethics committee of the University of Duisburg-Essen (Essen, Germany—19-8632-BO) and conformed to the principles of the Declaration of Helsinki.

Echocardiographic investigations were performed using an EPIQ 7 (Philips Healthcare, Hamburg, Germany) ultrasound machine. All echocardiographic examinations and measurements of cardiac structure and function were carried out according to the standard recommendations of the European Association of Cardiovascular Imaging and American Society of Echocardiography.[26–28] All echocardiographic images/loops were digitally stored, and echocardiographic parameters were measured.

Two-dimensional EF (2D-EF) was evaluated by the biplane method. Three-dimensional EF (3D-EF) was measured using the QLab software (Philips Healthcare, Hamburg, Germany). Pulsed-wave Doppler assessment of transmitral flow was obtained in the apical four-chamber view according to the guidelines.[26–28] LV myocardial velocities at the lateral segments of the mitral annulus during early diastole (e') were measured in the apical four-chamber view by tissue Doppler imaging, and the E/e' ratio was calculated for all participants.

Right ventricular fractional area change (FAC) was calculated from the apical four-chamber view using the percentage change in the RV end-diastolic and end-systolic areas using the formula: (end-diastolic area − end-systolic area)/end-diastolic area. Tricuspid annular plane systolic excursion (TAPSE) as marker of longitudinal RV function was measured by measuring the distance of systolic annular RV excursion at the tricuspid lateral annulus and along a longitudinal line defining the end of systole as the end of the T-wave. Pulmonary artery systolic pressure (PASP) was estimated by adding the pressure gradient between the right ventricle and right atrium to the central venous pressure. RV longitudinal strain of the free wall (RV-LSFW) was measured using speckle-tracking method and dedicated QLab software using the software settings for LV 4C view (Philips Healthcare, Hamburg, Germany) in a *post hoc* analysis. In brief, the endocardial border of the right ventricle was manually traced (~10 points) over one frame, and endocardial borders were automatically tracked throughout the cardiac cycles by the software. The software determines myocardial velocity as the ratio between frame-to-frame displacement of the speckles and the time interval and derives the systolic longitudinal strain. RV-LSFW was measured as the average of three segmental strain values (base, mid, and apex). LV-GLS was assessed in the same way using QLab software for LV 4C, 3C, and 2C views.

Right atrial (RA) measurements were performed in the apical four-chamber view. RA volume was calculated in the four-chamber view and indexed for BSA. For RA strain measurement, the apical four-chamber view in which the RA free wall best visualized was selected. Longitudinal strain measures were recorded in P–P intervals. In this P-wave trig-

ger method, the onset of P-wave is set as reference point as described previously.[29–31] The strain curve constructed from P-wave led to recognition of peak negative strain corresponding to RA strain during contraction phase (RASct) and peak positive strain corresponding to RA strain during conduit phase (RAScd). The sum of the absolute value of RA peak negative strain and RA peak positive strain corresponded to RA strain during reservoir phase (RASr).

Continuous variables were shown as mean ± standard deviation. Normal distribution was tested by Shapiro–Wilk test. For the parameters that showed normal distribution, the paired Student's *t*-test was used for detection of differences between examined time points. Non-parametric parameters were compared using the Wilcoxon test for dependent variables. The association between RV-LSFW and age, BMI, gender, hypertension, 2D-EF, and pulmonary pressure was assessed by univariate linear regression analysis in the whole study population. A *P*-value <0.05 was considered statistically significant.

Results

Baseline characteristics and clinical presentation

Baseline characteristics of the study population are provided in *Table 1*. The mean age of the patients was 59 ± 13 years. Forty percent of patients were female. The patients were treated with ICI therapy due to unresectable stage III (37%) or IV (63%) melanoma. Half of the patients received nivolumab single therapy, and the other half received a combination of nivolumab and ipilimumab. Baseline characteristics were not different comparing the different treatment groups (Supporting Information, Table *S1*). Three patients with known arterial hypertension showed increased blood pressure values before the start of ICI therapy. Those were treated with an increase dosage of their pre-existing blood pressure-lowering drugs [e.g. angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker]. There was no patient who was prescribed with a classical cardioprotective therapy regimen *de novo*. At follow-up time point, two patients had increased blood pressure, and they were treated with increased dosages of their pre-existing medication as well (ACE-I and calcium channel blockers).

Table 1 Baseline characteristics

Age (years)	59 ± 13
Female sex (%)	40
BMI (kg/m^2)	26.9 ± 4.2
Heart rate (b.p.m.)	72 ± 21
Haemoglobin (g/dL)	13.1 ± 1.9
Platelets (× 1000/μL)	308 ± 135
GFR (mL/min)	76 ± 20
CRP (mg/dL)	1.9 ± 4.5
Troponin I (ng/L)	15 ± 42
NT-proBNP (pg/mL)	126 ± 189
Comorbidities	
Arterial hypertension (%)	47
Diabetes (%)	9
Atrial fibrillation (%)	6
Known CAD (%)	6
Known CHF (%)	0
Premedication	
ACE-I/ARB (%)	41
Beta-blocker (%)	28
Aspirin/DAPT (%)	22
Tumour stage III (%)	37
Tumour stage IV (%)	63
ICI therapy regimen	
Nivolumab monotherapy (%)	50
Nivolumab/ipilimumab (%)	50

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CRP, C-reactive protein; DAPT, dual antiplatelet therapy; GFR, glomerular filtration rate; ICI, immune checkpoint inhibitor; NT-proBNP, N-terminal pro-brain natriuretic peptide.

Deterioration of right ventricular free wall strain after the start of immune checkpoint inhibitor therapy

Strain analyses of the RV free wall were performed before and 4 weeks after the start of ICI therapy. A significant deterioration of RV-LSFW after the start of ICI therapy was detected (−25.5 ± 6.4% to −22.4 ± 4.3%, $n = 27$, $P = 0.002$, *Table 2* and *Figure 1*). Deterioration of RV-LSFW was seen in both treatment groups (Supporting Information, *Figure S1*). Univariate linear regression revealed that only age was related with RV-LSFW in the whole study population (*Table 3*).

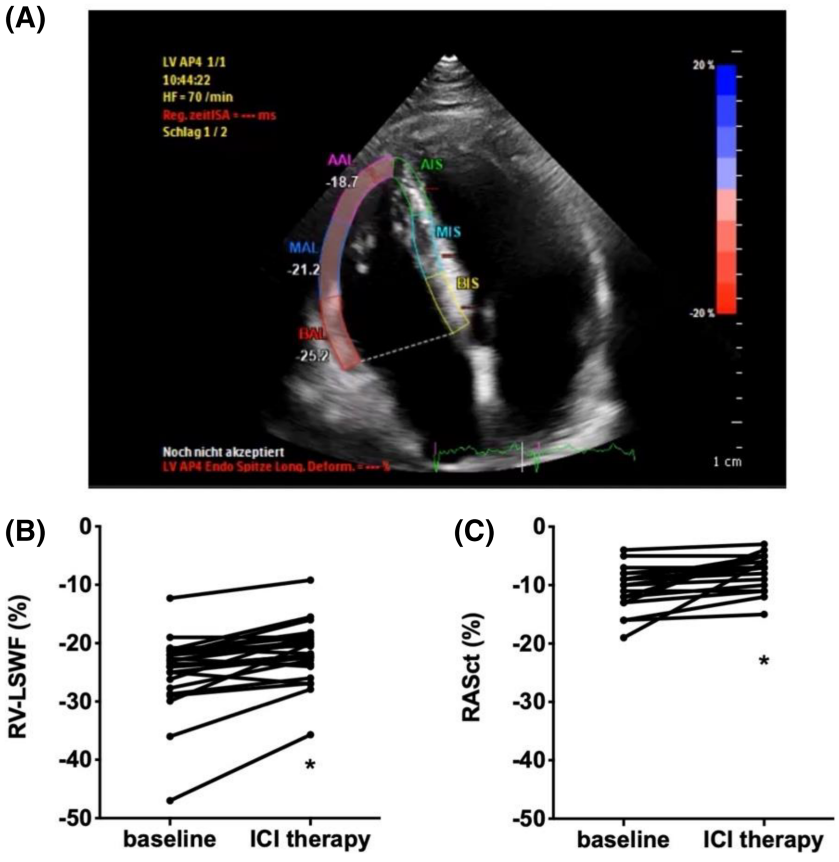
Conventional measures of RV function were assessed by TAPSE and FAC. There were no changes between the two assessment points (TAPSE 26 ± 5 vs. 25 ± 5 mm, $n = 25$, $P = 0.125$; FAC 38 ± 13% vs. 38 ± 14%, $n = 30$, $P = 0.750$, *Table 2* and *Figure 2*). The assessment of PASP showed similar values before and after ICI therapy start (27 ± 10 vs. 25 ± 8 mmHg, $n = 25$, $P = 0.268$, *Table 2* and *Figure 2*). RA linear dimensions were measured using a four-chamber view. There was no dilation of the right ventricle as measured by basal and mid-cavity diameters (basal RV diameter 38 ± 5 vs. 37 ± 6 mm, $n = 30$, $P = 0.103$; mid-cavity RV diameter 26 ± 5 vs. 25 ± 5 mm, $n = 30$, $P = 0.125$, *Table 2* and *Figure 2*). There were no differences in parameters of RV function comparing stage III and IV melanoma patients before therapy start or comparing stage III and IV melanoma patients separately before and after therapy start (data not shown). Echocardiographic parameters were not different comparing both treatment groups (Supporting Information, *Table S2*).

Table 2 Echocardiographic parameters of left and right ventricular structure, function, and mechanics

	At baseline	After ICI therapy	*P*
2D-EF (%)	59 ± 5	58 ± 6	0.654
3D-EF (%)	61 ± 6	60 ± 5	0.447
LVEDV (mL)	88 ± 27	83 ± 41	0.447
LVESV (mL)	36 ± 13	36 ± 29	0.980
LV-GLS (%)	−21.9 ± 1.7	−21.3 ± 1.3	0.171
LA volume index (mL/m^2)	25 ± 9	24 ± 8	0.676
E/A ratio	1.1 ± 0.3	1.2 ± 0.4	0.564
E/e'	7.4 ± 4.9	6.9 ± 4.8	0.165
Deceleration time (ms)	221 ± 63	197 ± 56	0.168
RV and RA parameters			
RV basal diameter (mm)	38 ± 5	37 ± 6	0.103
RV mid-cavity diameter (mm)	24 ± 4	24 ± 5	0.400
TAPSE (mm)	26 ± 5	25 ± 5	0.125
FAC (%)	38 ± 13	38 ± 14	0.750
PASP (mmHg)	27 ± 10	25 ± 8	0.263
RA volume index (mL/m^2)	18 ± 7	19 ± 7	0.508
RV and RA strain parameters			
RV-LSFW (%)	−25.5 ± 6.4	−22.4 ± 4.3	**0.001**
RASct (%)	−10.6 ± 3.9	−7.7 ± 3.1	0.001
RAScd (%)	40.4 ± 21.3	36.9 ± 16.5	0.570
RASr (%)	51 ± 23.1	44.7 ± 17.2	0.150

2D-EF, two-dimensional ejection fraction; 3D-EF, three-dimensional ejection fraction; FAC, fractional area change; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LV-GLS, left ventricular global longitudinal strain; PASP, pulmonary artery systolic pressure; RA, right atrial; RAScd, right atrial strain during conduit phase; RASct, right atrial strain during contraction phase; RASr, right atrial strain during reservoir phase; RV, right ventricular; RV-LSFW, right ventricular longitudinal strain of the free wall; TAPSE, tricuspid annular plane systolic excursion.
All values are mean ± standard deviation.

Figure 1 Strain analysis of the right heart. (A) Example on the assessment of right ventricular longitudinal strain of the free wall (RV-LSFW) using Philips software. (B) RV-LSFW before and after the start of immune checkpoint inhibitor (ICI) therapy. (C) Right atrial strain during contraction phase (RASct) shows significant deterioration after ICI therapy.



DOI: 10.1002/ehf2.14094

Table 3 Univariate regression analysis

Parameters	RV free wall strain			RA strain during contraction phase		
	R^2	95% CI	*P*	R^2	95% CI	*P*
Age (years)	0.191	0.116–2.502	0.033	0.052	−0.976 to 2.744	0.331
BMI (kg/m^2)	0.137	−0.066 to 0.539	0.117	0.021	−0.352 to 0.622	0.565
Gender (F)	0.025	−2.638 to 5.297	0.292	0.061	−1.681 to 5.328	0.290
Hypertension	0.098	−1.179 to 6.383	0.166	0.010	−4.025 to 2.994	0.761
2D-EF (%)	0.027	−0.334 to 0.675	0.486	0.391	0.283–1.518	0.007
PASP (mmHg)	0.013	−0.703 to 1.121	0.635	0.180	−0.212 to 2.122	0.101

2D-EF, two-dimensional ejection fraction; BMI, body mass index; CI, confidence interval; PASP, pulmonary artery systolic pressure; RA, right atrial; RV, right ventricular.

Deterioration of right atrial strain after the start of immune checkpoint inhibitor therapy

The right atrium was examined by measuring the RA volume index and RA strain values. Only RASct showed significant deterioration after 4 weeks of ICI therapy (−10.6 ± 3.5% vs. −7.7 ± 3.1%, *n* = 20, *P* = 0.001, *Table 2* and *Figure 1*), indicating a decreased pump function of the right atrium. Similar results were shown in patients with nivolumab monotherapy and also in the group that received nivolumab/ipilimumab combination therapy (Supporting Information, *Figure S1*). Univariate linear regression revealed that only 2D-EF was related with RASct in the whole study population (*Table 3*). RAScd and RASr were similar before and after ICI therapy (RAScd 40.4 ± 21.3% vs. 36.9 ± 16.5%, *n* = 20, *P* = 0.570; RASr 51 ± 23.1% vs. 44.7 ± 17.2%, *n* = 20, *P* = 0.150, *Table 2* and *Figure 1*). Comparable with RV linear dimensions, there was no change in RA volume index (18 ± 7 vs. 19 ± 7 mL/m^2, *n* = 25, *P* = 0.508, *Table 2* and *Figure 2*).

No alterations in left ventricular parameters and cardiac biomarkers after the start of immune checkpoint inhibitor therapy

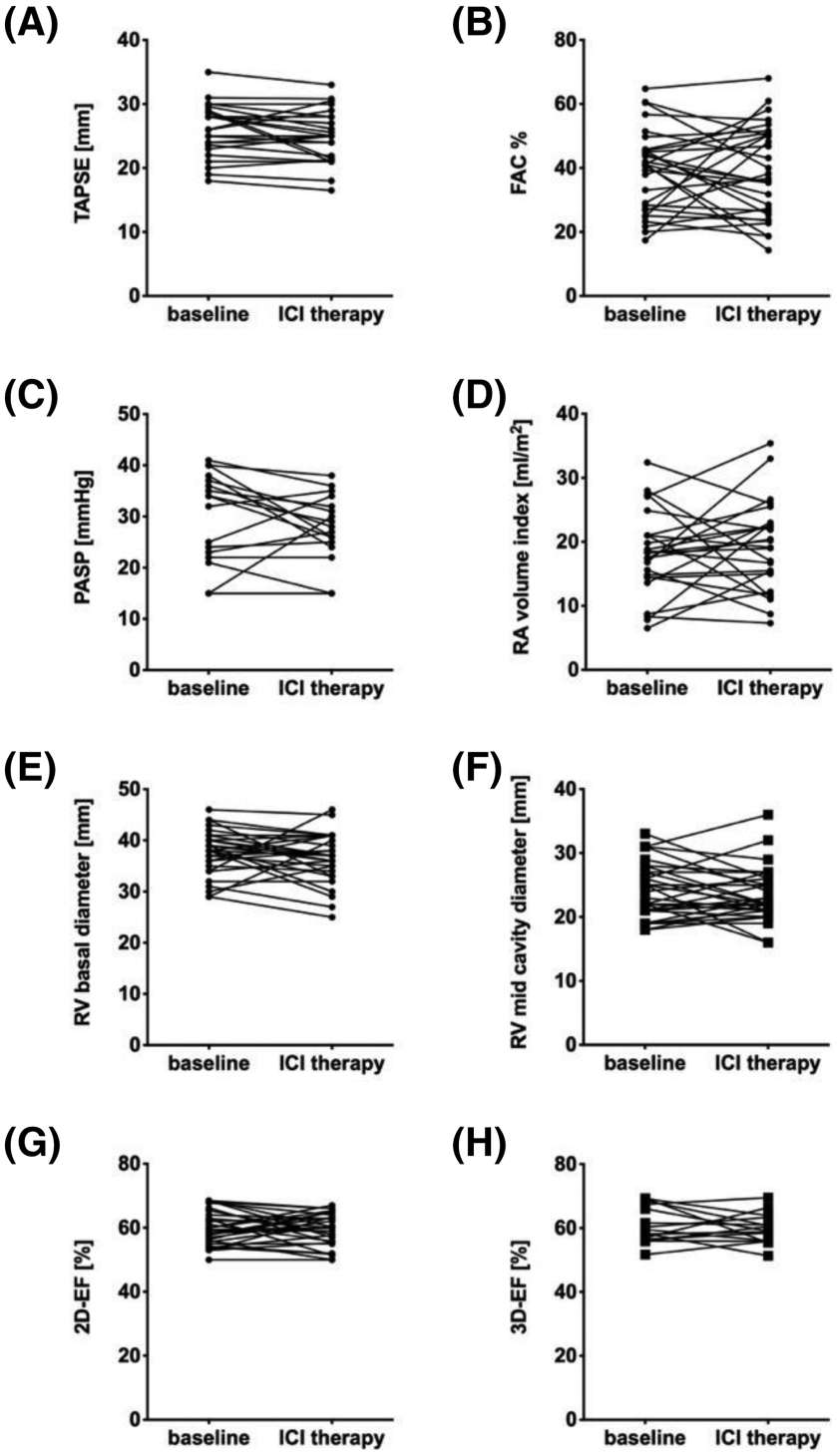
Left ventricular end-diastolic and end-systolic volumes were similar before and after the start of ICI therapy (LV end-diastolic volume 88 ± 27 vs. 83 ± 41 mL, *n* = 30, *P* = 0.447; LV end-systolic volume 36 ± 13 vs. 36 ± 29 mL, *n* = 30, *P* = 980, *Table 2*). There was no change in 2D-EF and 3D-EF after the start of ICI therapy (2D-EF 59 ± 5% vs. 58 ± 6%, *n* = 30, *P* = 0.654; 3D-EF 61 ± 6% vs. 60 ± 5%, *n* = 22, *P* = 0.447, *Table 2* and *Figure 2*). LV strain analysis showed equal values for LV-GLS at both time points (−21.9 ± 1.7% vs. −21.3 ± 1.3%, *n* = 22, *P* = 0.1705). LV diastolic function was assessed following a standard protocol with measurements of E/A, lateral e' velocity, and deceleration time.[26] None of the parameters showed changes comparing values before and after the start of ICI therapy (E/A 1.1 ± 0.3 vs. 1.2 ± 0.4, *n* = 24, *P* = 0.564; E/e' 7.4 ± 4.9 vs. 6.9 ± 4.8, *n* = 24, *P* = 0.165; and deceleration time 221 ± 63 vs. 197 ± 56 ms, *n* = 24, *P* = 0.168, *Table 2*). Left atrial (LA) volume did not dilate after ICI therapy start (LA volume index 25 ± 9 vs. 24 ± 8 mL/m^2, *n* = 30, *P* = 0.676, *Table 2*). There were no differences in parameters of LV function comparing stage III and IV melanoma patients and comparing stage III and IV melanoma patients separately before and after therapy start (data not shown). Because the assessment of cardiac biomarkers is one of the key parameters in the detection of cardiotoxicity, we compared troponin I values before and after the start of ICI therapy. There was no significant troponin I elevation in the follow-up laboratory (baseline 15 ± 42 ng/L vs. follow-up 5 ± 8 ng/L, *n* = 30, *P* = 0.1523, data not shown). N-terminal pro-brain natriuretic peptide levels remained without significant elevation as well (baseline 126 ± 189 ng/L vs. follow-up 115 ± 104 ng/L, *n* = 25, *P* = 0.8333, data not shown). No patient was suspected to have immune-related cardiovascular toxicity at the follow-up time point in regard to the diagnosis criteria suggested by the European Society of Cardiology.

Discussion

The present study evaluates right heart function in melanoma patients undergoing ICI therapy. We here provide the following findings: first, longitudinal strain of the RV free wall was significantly impaired in patients during ICI therapy compared with values before therapy start. Second, ICI therapy deteriorates RASct, which corresponds to RA contractile function. Third, RV diameters and systolic function, assessed by conventional echocardiographic methods, were not deteriorated after short-term ICI therapy.

Over the last years, it has been forwarded that RV function has an important prognostic role in the course of many heart diseases, for example, systolic LV heart failure and coronary artery disease.[32–34] The echocardiographic assessment of the right ventricle by conventional 2D echocardiography remains challenging because of its retrosternal position and its complex geometry.[24] In the setting of toxicity from cancer therapy, early detection of subclinical cardiotoxicity is necessary to discuss modification of cancer treatment or initiate cardioprotective therapies.[35,36] To date, cardiotoxicity is de-

Figure 2 Conventional right and left heart parameters. Conventional parameters for right heart function like (A) tricuspid annular plane systolic excursion (TAPSE), (B) fractional area change (FAC), (C) pulmonary artery systolic pressure (PASP), (D) right atrial (RA) volume index, (E) right ventricular (RV) basal diameter, (F) RV mid-cavity diameter, and conventional parameters of left ventricular (LV) function assessed by (G) two-dimensional ejection fraction (2D-EF) and (H) three-dimensional ejection fraction (3D-EF) did not show changes comparing values before and after the start of immune checkpoint inhibitor (ICI) therapy.



DOI: 10.1002/ehf2.14094

fined by changes of the LV EF and/or LV global strain analyses, while right heart parameters are not part of the definition of cardiotoxicity.[20] While typical parameters of RV function, for example, FAC, S', or TAPSE, do not seem to be useful in reflecting early changes of right heart function and/or do not reflect global RV function, deformation imaging techniques (strain or strain rate imaging) of the right ventricle and right atrium seem to be as promising as they are for detection of early changes of LV function. Similar to LV strain, RV assessment by speckle-tracking methods allows the assessment in a non-geometrical manner, relatively independent of tethering or translational motion.[37,38] Reference values for RV-LSFW measures have been described to range between −21.7 ± 4.2% and −28.5 ± 4.7% depending on age, gender, and ultrasound vendor.[39] The values determined in this study fit into this range of reference values, even those after the start of ICI therapy. In contrast to LV strain analyses, there are no thresholds indicating cardiotoxic effects with regard to RV-LSFW values or other parameters of right heart function.

Assessment of RA parameters is of clinical importance because enlargement of the right atrium can reflect disturbed RV function and has been associated with poor clinical outcome.[40] Previous studies have identified RA strain as a sensitive prognostic measure in patients with congestive heart failure and pulmonary hypertension, but so far, there are no data on the impact of RA strain in the setting of cancer of cardiotoxicity. Negative atrial strain is a parameter of contractile RA function. In patients with pulmonary artery hypertension, the RA contractile function represented by atrial strain measures was used as a marker of severity of right heart dysfunction.[41]

Immune checkpoint inhibitor therapy is known to induce severe irAEs. Of all irAEs, cardiotoxicity is associated with the highest mortality rates. To date, little is known about the underlying pathomechanisms. In a mouse model, it was recently shown that anti-PD1 therapies affect cardiac integrity by disrupting immune homeostasis and by inducing dysregulated metabolism including the proteome and lipidome. The resulting impaired LV stress tolerance was seen similarly in patients undergoing ICI therapy.[42] The clinical manifestation of immune-related cardiotoxicity is variable and includes myocarditis, perimyocarditis, pericarditis, LV dysfunction without myocarditis, coronary spasms, arrhythmias, and myocardial infarction.[43–45] Because of the lack of consistency of its clinical manifestation, diagnosis of immune-related cardiotoxicity is challenging. New data show that the analyses of electrocardiogram, cardiac biomarkers, and cardiac magnetic resonance imaging and echocardiographic assessment of myocardial function are of great importance.[16,46–49] Because of the high mortality of immune-related cardiotoxicity, its early detection seems of great importance. New parameters, which could indicate early cardiotoxicity, are therefore desirable. Our data show that changes in RA and RV mechanics already occur 4–6 weeks after administration of ICI therapies, while LV-GLS was stable without significant change at both time points (baseline vs. follow-up 4–6 weeks after ICI therapy start). Because the right ventricle is known to provide a smaller myocardial mass and thinner walls compared with the left ventricle,[23] it reacts faster to volume and haemodynamic changes. This could explain its higher susceptibility to the administration of ICIs compared with the left ventricle. The assessment of RV and RA function may serve as a new, potent tool for early detection of cardiac dysfunction. Prospective studies are now needed to determine whether the echocardiographic assessment of RA function serves to predict cardiotoxicity and whether changes in anticancer treatments or the start of cardioprotective therapies improves and/or preserves the right heart function. Although previous studies reported higher incidences of irAEs in patients receiving ICI combination therapies, RV-LSFW and RASct were deteriorated in both treatment groups.[16] This finding was unexpected at first sight, but of course, the isolated measurement of right heart strain parameters is not sufficient for the diagnosis of immune-related cardiovascular toxicity. The association of RV-LSFW and RASct with irAEs has to be proven.

The study has several limitations. First, because of the retrospective design of this study, it was not always possible to measure all parameters of LV and RV function, for example, due to the lack of the applied technique (RV tissue Doppler or 3D technology) or due to insufficient image quality. Second, the number of patients in our study is only 30, which represents a major limitation of this study. The limitation by the low patient number and the retrospective design was the basis for the establishment of our prospective registry with increased patient numbers and prespecified follow-up time points, which will be finished for analysis soon. Third, the follow-up period was short. Patients were evaluated after 4–6 weeks of ICI therapy. Although median time to onset of cardiovascular complications after the start of ICI therapy has been described to be within 34 days ranging from 21 to 75 days[16] and deteriorations in strain measurements of the RV free wall were already detectable in this time interval, it would be interesting to measure RV parameters in a long-term follow-up after 1 or 2 years of ICI therapy. Fourth, we cannot provide any mechanistical insight into the relationship between ICI therapy and right heart strain deterioration. Although several studies showed a reduction of RV strain in breast cancer and lymphoma patients undergoing anticancer therapies, the mechanism of subclinical RV dysfunction has not been elucidated yet. One could, for example, suspect that a fluid overload after anticancer therapies could influence right heart function, but ICI therapy is an anticancer therapy with a low infusion volume and conventional echocardiographic right heart parameters susceptible for a fluid overload were not different between both time points.

Further studies will be required to confirm the impact of ICI therapy on right heart function, its consequences for conducting the therapy, and whether this represents an early marker of cardiotoxicity.

Funding

T.R. was funded by the German Research Foundation [Deutsche Forschungsgemeinschaft (DFG)] (RA 964/12-2). S. M.M. and L.M. were supported by the IFORES research grant, Medical Faculty, University Duisburg-Essen, Essen, Germany.

Acknowledgements

Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest

None declared.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics comparing Nivolumab monotherapy and Nivolumab/Ipilimumab combination therapy groups.

Table S2. Echocardiographic parameters of left and right ventricular structure, function and mechanics comparing Nivolumab monotherapy group with Ipilimumab/Nivolumab combination therapy group.

Figure S1. Strain analysis of the right heart. RV-LSFW was significantly reduced after start of ICI therapy in patients undergoing (A) Nivolumab monotherapy and in patients undergoing (B) Nivolumab/Ipilimumab combination therapy. RA strain during contraction phase (RASct) shows significant deterioration after ICI therapy in patients undergoing (C) monotherapy and in those undergoing (D) combination therapy.

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DOI: 10.1002/ehf2.14094
URN: urn:nbn:de:hbz:465-20231124-163925-7