Utilizing Left Atrial Strain to Identify Patients at Risk for Atrial Fibrillation on Ibrutinib

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Abstract

Background: Ibrutinib is associated with atrial fibrillation (AF), though echocardiographic predictors of AF have not been studied in this population. We sought to determine whether left atrial (LA) strain on transthoracic echocardiography could identify patients at risk for developing ibrutinib-related atrial fibrillation (IRAF). Methods: We performed a retrospective review of 66 patients who had an echocardiogram prior to ibrutinib treatment. LA strain was measured with TOMTEC Imaging Systems, obtaining peak atrial longitudinal strain (PALS) and peak atrial contraction strain (PACS) on 4-chamber and 2-chamber views. Statistical analysis was performed with Chi-square analysis, T-test, or binomial regression analysis, with a p-value < 0.05 considered statistically significant. Results: Twenty-two patients developed IRAF (33%). Age at initiation of ibrutinib was significantly associated with IRAF (65.1 years vs. 74.1 years, $p = 0.002$). Mean ibrutinib dose was lower among patients who developed IRAF (388.2 ± 121.7 vs. 448.6 ± 88.4, $p = 0.025$). E/e' was significantly higher among patients who developed IRAF (11.5 vs. 9.3, $p = 0.04$). PALS was significantly lower in patients who developed AF (30.3% vs. 36.3%, $p = 0.01$). On multivariate regression analysis, age, PALS and PACS were significantly associated with IRAF. On multivariate regression analysis, only PACS remained significantly associated with IRAF while accounting for age. Conclusions: Age, ibrutinib dose, E/e', and PALS on pre-treatment echocardiogram were significantly associated with development of IRAF. On multivariate regression analyses, age, PALS and PACS remained significantly associated with IRAF. Impaired LA mechanics add to the assessment of patients at risk for IRAF

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Running Title : LA strain & ibrutinib-related atrial fibrillation

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Conclusions:

Age, ibrutinib dose, E/e', and PALS on pre-treatment echocardiogram were significantly associated with development of IRAF. On multivariate regression analyses, age, PALS and PACS remained significantly associated with IRAF. Impaired LA mechanics add to the assessment of patients at risk for IRAF.

Keywords :

- Echocardiography
- Left atrial strain
- Atrial fibrillation
- Ibrutinib
- Tyrosine kinase inhibitor
- B-cell malignancies

Introduction:

Ibrutinib is an irreversible Bruton tyrosine kinase inhibitor used in the treatment of various B-cell malignancies, including chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), relapsed or refractory Mantle cell lymphoma, relapsed or refractory marginal zone lymphoma, Waldenstrom macroglobulinemia, chronic graft-versus-host disease and additional off-label uses [1, 2]. Ibrutinib has been associated with the development of atrial fibrillation (AF) in approximately 6-16% of patients [1], though a recent prospective multicenter cohort study suggests the incidence of ibrutinib-related atrial fibrillation (IRAF) may be as high as 38% at 2 year follow up [3]. A systematic review and meta-analysis of four randomized control

trials noted the pooled relative risk of AF in ibrutinib recipients was 3.5 (95% confidence interval 1.8-6.9, $p < 0.0001$) [4]. Cardiovascular adverse events related to ibrutinib were associated with a 10-20% fatality rate (with the exception of ibrutinib-associated hypertension), as per a retrospective international analysis of 303 ibrutinib-associated cardiovascular deaths [5].

Various studies have sought to identify risk factors that predict future development of IRAF. In a large study of 4 randomized control trials, 1505 patients with CLL and Mantle cell lymphoma, a multivariate analysis showed that use of ibrutinib, prior history of AF and age > 65 were associated with higher risk of AF [1]. A retrospective analysis demonstrated a history of AF and higher Framingham Heart Study AF risk score were significantly associated with IRAF [6]. Another retrospective analysis noted that among various clinical, electrocardiographic, and echocardiographic parameters, only the presence of left atrial (LA) abnormality on electrocardiogram and prior history of heart failure were independently associated with IRAF in a paired Cox regression model [2]. A prospective analysis of 43 patients receiving ibrutinib for CLL demonstrated that male gender, the presence of one or more cardiac comorbidities, LA diameter and LA area on transthoracic echocardiogram predicted future development of IRAF [7]. These studies highlight the need to better identify clinical and echocardiographic parameters to reliably stratify the risk of IRAF.

Two-dimensional speckle tracking echocardiography (2DSTE) provides a quantitative measure of myocardial deformation, and there is growing use of STE in analyzing LA deformation, measured as LA strain [8]. LA strain is measured across the cardiac cycle and averaged between four- and two-chamber apical views. Peak atrial longitudinal strain (PALS), is measured immediately following atrial filling, with a normal reference range across healthy adults of approximately 39% (95% CI 38-41%) [9, 10]. Peak atrial contraction strain (PACS), is measured immediately prior to atrial contraction, with a normal reference range of 17% (95% CI 16-19%) [9, 10]. Conduit strain is defined as the difference between PALS and PACS, with a normal reference range of 23% (95% CI 21-25%). Current work suggests LA strain may hold predictive value for the development of AF [11]. We sought to identify whether LA strain is associated with development of AF for patients on ibrutinib therapy.

Material and Methods:

Study Subjects

The Northwestern Medicine Enterprise Data Warehouse was queried to identify all patients who were prescribed ibrutinib between July 2012 and July 2016, and received primary oncologic care at our institution. Patients were aged 18 to 90 years old, and all patients with a prior history of AF were excluded. One hundred sixty-nine patients were initially identified. Of these patients, those who had a transthoracic echocardiogram prior to initiation of ibrutinib therapy were included, yielding a total 75 patients. Nine patients were excluded because echocardiographic images were not available for review on Northwestern software, yielding a total 66 patients.

Demographic information was collected through a retrospective chart review of each patient's electronic medical record, including gender, race, age of patient at initiation of ibrutinib, and body mass index (BMI). Comorbidities included hypertension (HTN), hyperlipidemia (HLD), diabetes (DM), coronary artery disease (CAD) and clinical history of heart failure (HF) prior to initiation of ibrutinib. Information regarding ibrutinib dose, length of follow up, rates of CVA among patients who developed IRAF and rates of anticoagulant and antiplatelet use for patients with IRAF were also noted. Duration of follow up was defined as either time to development of AF, time until last follow up, or time until patient death. The Northwestern University institutional review board approved this study.

Transthoracic Echocardiography

Echocardiographic measurements were obtained according to the American Society of Echocardiography guidelines [12] on GE or Phillips machines. Two blinded reviewers retrospectively analyzed the transthoracic echocardiograms of all patients prior to ibrutinib treatment, obtaining measures of right atrial pressure, right ventricular size (RV size), right ventricular fractional area change, right ventricular systolic pressure,

tricuspid regurgitation maximum velocity (TR Vmax), TAPSE, left atrial indexed volume (LAVI), mitral E and A velocity, mitral E/e', diastolic dysfunction, valvular disease, left ventricular ejection fraction (LVEF) and left ventricular global longitudinal strain (LV GLS). RV size was measured as RV basal diameter at end diastole in the apical 4 chamber view. LAVI was measured using the biplane area-length method. Valvular disease was noted if patients had moderate or severe mitral stenosis, mitral regurgitation, aortic stenosis or aortic regurgitation.

Two-Dimensional Speckle-Tracking Echocardiography

Commercially available software (TOMTEC Imaging Systems, Munich, Germany) was used to obtain 2DSTE at frame rates between 40 to 80 frames/sec. Left ventricular GLS was obtained in the standard 2-, 3-, and 4-chamber apical views by averaging the peak systolic strain in all segments. A third, blinded reviewer analyzed LA strain on TOMTEC, including measures of PALS and PACS. PALS was measured in 4- and 2-chamber views, the values of which were averaged to determine mean PALS. Similarly, PACS was measured across 4- and 2-chamber views, and averaged to determine mean PACS. Conduit strain was calculated as the difference between PALS and PACS.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Version 26 (Chicago, IL). Baseline patient characteristics were evaluated across patient groups; categorical variables were analyzed using Chi-square testing, and continuous variables were analyzed by two-tailed t-tests. Univariate and multivariate regression analyses were used to determine whether specific clinical and echocardiographic parameters could identify patients at risk for developing AF.

Intra- and Inter-observer Variability

The intra- and inter-observer variability were calculated as the intraclass correlation coefficient (ICC) for measures of PALS and PACS in 2- and 4-chamber views across 8 randomly selected patients. Intra-observer variability was calculated based on repeated LA strain measures by the same echocardiographer blinded to prior measurements, and interobserver variability was performed by a second echocardiographer blinded to prior measurements.

Results:

Among 66 patients who had echocardiograms prior to ibrutinib initiation, 22 developed AF (33.3%). Patients were followed for a mean 2.8 years. Forty-three patients were male (65.2%) and 23 were female (34.8%). The mean patient age at the time of ibrutinib initiation was 68 years. Patients who developed IRAF were significantly older at the time of ibrutinib initiation (74.1 years vs. 65.1 years, $p = 0.002$). Mean ibrutinib dose was 428.5mg, and patients who developed IRAF received significantly lower doses of ibrutinib (388.2mg vs. 448.6mg, $p = 0.025$). Approximately half (53.0%) of patients were being treated for CLL/SLL, whereas 28.8% of patients had other lymphomas (including mantle cell lymphoma, diffuse large B cell lymphoma, follicular lymphoma and MALT lymphoma) and 16.7% had a plasma cell dyscrasia (Waldenstrom's macroglobulinemia, multiple myeloma, or MGUS). Notably, the baseline rate of HF for this population was higher than the general population at 15.2%, though rates of HF were not significantly different between patients with and without IRAF (27.3% for patients with IRAF, 9.1% for patients without IRAF, $p = 0.052$). Among 10 patients who had a history of HF and developed IRAF, 6 patients had preserved ejection fraction and 4 patients had a reduced ejection fraction. Sixty-one patients (92.4%) had EKGs prior to initiation of ibrutinib, and 9 of these had left atrial enlargement (LAE) by EKG. The presence of LAE on EKG was not significantly associated with development of AF. Additional baseline characteristics of the patient population are shown in **Table 1** .

Among the 22 patients who developed IRAF, only 6 were placed on anticoagulation (27.3%) and 4 (18.2%) were placed on antiplatelet therapy. Two patients (9.1%) were on both anticoagulation and antiplatelet

therapy. Twenty patients (90.9%) had paroxysmal AF, and two patients (9.1%) had persistent AF. Both patients with persistent AF were on anticoagulation. In most cases, anticoagulation was deferred given a low CHA_2DS_2-VASc score or a single, self-limited event of AF. Eleven patients with AF (50%) were symptomatic at the time of AF detection. No patients with AF developed ischemic or embolic strokes during follow up. One patient developed an intraparenchymal hemorrhage, and was diagnosed with new-onset AF at the time of presentation for intraparenchymal hemorrhage. This patient had not been on anticoagulation or antiplatelet therapy previously, and had a CHA_2DS_2-VASc score of 3.

Baseline echocardiographic parameters were obtained prior to initiation of ibrutinib. LAVI was higher in patients who developed IRAF, though not statistically significant (32.2 vs. 27.1, p = 0.07). E/e' was significantly higher among patients who developed IRAF (11.5 vs. 9.3, p = 0.04). Left ventricular EF was not significantly different between patient groups (62.7% vs. 61.7%, p = 0.63). Additional baseline echocardiographic measures, including right atrial pressure, TR Vmax, TAPSE, right ventricular size, right ventricular fractional area change, right ventricular systolic pressure, E velocity, A velocity and LV GLS were not significantly different between patient groups, as seen in**Table 2** .

Mean PALS was 34.2% ± 9.0 across all patients. Mean PACS was 17.3% ± 5.2, and mean conduit strain was 17.1% ± 6.8. PALS was significantly lower in patients who developed IRAF (30.3% vs. 36.3%, p = 0.01). PACS was lower in patients who developed AF, though this did not reach statistical significance (15.6% vs. 18.2%, p = 0.06). Conduit strain was lower among patients who developed IRAF, though not statistically significant (15.0% vs. 18.3%, p = 0.07). Results comparing PALS, PACS and conduit strain are shown in **Table 3** . Intra-observer ICC was 0.86 (95% CI 0.72-0.93) and inter-observer ICC was 0.90 (95% CI 0.80-0.95) for measures of LA strain.

Univariate Regression

Age remained significantly associated with IRAF on univariate regression analysis (OR 3.21, p = 0.002). Ibrutinib dose remained significantly associated with IRAF (OR -2.30, p = 0.025). E/e' and PALS were both significantly associated with IRAF on univariate regression modeling (OR = 2.1, p = 0.04; OR = -2.7, p = 0.01, respectively). Neither PACS or conduit strain were significantly associated with IRAF on univariate regression.

Multivariate Regression

Age, ibrutinib dose, E/e', PALS, PACS, and conduit strain were analyzed as pairs on Cox regression modeling given the low number of events. On multivariate regression modeling of age and ibrutinib, age and E/e', age and PALS, and age and conduit strain, only age remained significant for association with IRAF. When age and PACS were evaluated, both remained significant for association with IRAF (p = 0.002 for age, p = 0.04 for PACS). On multivariate regression analysis of ibrutinib dose and PALS, and ibrutinib dose and PACS, both PALS and PACS significant for association with IRAF (p = 0.008 and p = 0.05, respectively). Additional multivariate regression analyses are shown in **Table 4** .

Discussion:

LA mechanics are increasingly important prognostic markers of AF development. We applied measures of PALS and PACS to a unique cohort of patients who have a well-recognized risk of developing AF on ibrutinib. This is the first study to demonstrate that measures of LA strain prior to initiation of ibrutinib therapy help identify patients at risk for developing IRAF. On univariate analysis, age, ibrutinib dose, E/e', and PALS were associated with IRAF. On multivariate regression analysis, age and PACS had notably strong associations with IRAF. On multivariate regression analyses of ibrutinib dose and echocardiographic parameters, both PALS and PACs were associated with IRAF.

The pathophysiology of IRAF is as yet unknown [13]. Experimental studies on rat models suggest ibrutinib activity inhibits the PI3K-Akt signaling pathway in cardiac myocytes, which increases susceptibility to AF [14]. Further work with mouse models has suggested that ibrutinib induces structural remodeling and calcium handling disorders in atria, leading to increased arrhythmogenicity [15]. Additional work has

suggested the possibility of a two-hit hypothesis, due to which patients with structural abnormalities are increasingly susceptible to PI3K-Akt downregulation by ibrutinib [2]. Our findings corroborate this theory, as they indicate a relationship between impaired LA myocardial mechanics prior to ibrutinib initiation and subsequent IRAF. This highlights opportunities for translational studies of patients with abnormal LA strain and investigating underlying mechanisms of IRAF.

A meta-analysis of LA strain across healthy adults estimated PALS is approximately 39% (38-41) across 40 studies and PACS is 17% (16-19) across 18 studies [9]. Our patient population had a lower than average PALS of 34.2%, and a PACS of 17.3%, which approximated that of this meta-analysis. We suspect the decreased average PALS of our patient population reflects increased baseline population rates of concomitant heart failure and other cardiac comorbidities. **Figure 1** shows LA strain mechanics of two patients in our cohort: a patient without AF who has normal PALS and PACS, versus a patient with IRAF with decreased PALS and PACS. This figure delineates the patient who develops IRAF has notable loss of a well-defined atrial contraction pattern, calculated as PACS, which predates the occurrence of IRAF.

PALS was significantly associated with IRAF on univariate regression analysis, though was not significant on multivariate analyses when accounting for patient age. We suspect that while PALS is an echocardiographic marker associated with IRAF, impairment in PALS may be a function of increasing population age and other comorbidities. In contrast, PACS was not associated with IRAF on univariate analysis, though had a significant association with IRAF in multivariate regression modeling with age. This suggests that impaired PACS can identify patients with poorer atrial contractile function, which predisposes them to the development of IRAF independent of patient age. Taken together, the relationship between these measures of LA strain and IRAF suggests that significant impairments in LA mechanics detect LA myopathy, which may predispose patients to the development of IRAF.

LA strain may be able to discern various cardiac pathologies, though further work remains to be done within this realm [16]. One study of patients with non-ischemic cardiomyopathy noted decreased PACS was an independent and incremental predictor of ventricular arrhythmia [17]. It was proposed that in diseased ventricular states, PACS has increased importance as it helps maintain cardiac output and control pulmonary capillary wedge pressure [17]. The relationship between LA mechanics, IRAF and concurrent HF merits further evaluation. In our work, patients who developed IRAF had increased E/e', which may suggest the presence of subclinical HF. Both PALS and PACS demonstrated stronger associations with the development of IRAF than E/e'. However, the impact of HF and elevated filling pressures on impaired LA mechanics in the development of IRAF needs to be further explored.

Prior work has suggested the importance of PALS in patients with AF, as this specifically reflects atrial compliance [11]. Studies have indicated a relationship between PALS and risk of stroke in patients with permanent AF [18] as well as a relationship between improved PALS and maintenance of sinus rhythm after AF ablation [19]. Of note, PACS can only be measured in patients with sinus rhythm, and it is thought that in adults without a history of atrial arrhythmia, impaired PACS may reflect the initial structural remodeling which ultimately leads to the development of AF [20]. Our work suggests a complex interplay of both these measures of LA strain, as related to age and other comorbidities in the development of IRAF.

Management of IRAF poses unique challenges given the increased risk of bleeding associated with ibrutinib and various medication interactions [21, 22]. It is estimated that ibrutinib is associated with bleeding in 3-5% of patients, likely mediated by platelet dysfunction [23], and potentially compounded by underlying thrombocytopenia in the setting of hematologic malignancy [24]. The majority of ibrutinib-related bleeding events tend to be mild and do not require medication interruption or dose modification [23]. However, this known bleeding risk complicates decisions regarding initiation of anticoagulation and procedural intervention for IRAF. It is worth noting that one patient in our cohort who developed IRAF had a concurrent intraparenchymal hemorrhage, not on any anticoagulation or antiplatelet therapy. Furthermore, ibrutinib is primarily metabolized by hepatic cytochrome P450 3A4 which complicates choice of anticoagulant given known metabolic interactions [24]. Better understanding of AF risk, incorporating clinical and echocardiographic variables such as LA strain, may inform anticoagulation management and warrants further exploration.

As a retrospective analysis, our work carries a risk of selection bias. Specifically, at the time during which our patients were initiated on ibrutinib, there were no specific guidelines for echocardiographic screening prior to treatment. Therefore, patients who had echocardiograms within our database likely had concern for underlying cardiac pathology, as suggested by the high baseline rate of HF seen in our population. Our work also demonstrates an inverse relationship between ibrutinib dose and IRAF rate. Ibrutinib dose was decreased for patients who demonstrated intolerance to higher doses due to a variety of adverse events (neutropenia, GI symptoms), and these patients may have been more likely to develop cardiac toxicity as well. We recognize that the specific strain values used in this study apply to our population and strain software, and may not be universally translated, owing to the software-dependent variability of strain findings.

Our study was limited by a small patient population, though notably within which 33.3% of the population developed IRAF. Larger studies will assist in validating the relationship between LA strain and IRAF, and determining predictive markers which have greater sensitivity for detecting IRAF. Our findings suggest a complex interplay between age, ibrutinib dose, LA myocardial dynamics and IRAF, which merits further prospective evaluation. Results are forthcoming from the CITE-LA trial (NCT03751410), a prospective, observational cohort study assessing LA strain of patients on chronic ibrutinib therapy, which may elucidate this relationship further [25].

Conclusions:

Age, ibrutinib dose, E/e', and PALS on pre-treatment echocardiogram were significantly associated with the development of IRAF. On multivariate regression analysis, age, PALS and PACS remained significantly associated with the development of IRAF. PALS may demonstrate an age-dependent association with IRAF, whereas PACS may represent age-independent loss of atrial contraction. Future studies are needed to determine if this information can identify increased risk of IRAF, need for enhanced surveillance, adjustment in anticoagulation management, and possibly alternate oncologic therapies.

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Tables

Table 1: Baseline Clinical Characteristics of Patients on Ibrutinib

	Total Sample (n = 66) *Mean ± SD or %, (n)*	**No Atrial Fibrillation (n = 44)** *Mean ±*
Age*	68.1 ± 11.5 (66)	65.1 ± 11.1 (44)
Ibrutinib Dose*	428.5 ± 103.8 (66)	448.6 ± 88.4 (44)
BMI	27.5 ± 5.8 (66)	28.1 ± 6.3 (44)
Sex, % (n)		
Male	65.2 (43)	61.4 (27)
Female	34.8 (23)	38.6 (17)
Race/Ethnicity, % (n)		
Non-Hispanic White	74.2 (49)	77.3 (34)
Non-Hispanic Black	7.6 (5)	6.8 (3)
Other/Unknown	18.2 (12)	15.9 (7)
Comorbidities, % (n)		
HTN	77.3 (51)	79.5 (35)
HLD	65.2 (43)	61.4 (27)
DM	28.8 (19)	13.6 (6)
CAD	19.7 (13)	15.9 (7)
HF	16.7 (10)	9.1 (4)
MR	1.5 (1)	0.0 (0)
AS	1.5 (1)	0.0 (0)
Malignancy, % (n)		
CLL/SLL	53.0 (35)	(22)
Other Lymphoma	28.8 (19)	(14)
Plasma Cell Dyscrasia	16.7 (11)	(8)
Other	1.5 (1)	(0)

***** : $p < 0.05$. Age was significantly higher for patients in AF group, $p = 0.002$. Ibrutinib dose was significantly lower among patients who developed AF, $p = 0.025$. HTN: hypertension. HLD: hyperlipidemia. DM: diabetes mellitus. CAD: coronary artery disease. HF: history of heart failure. MR: moderate or severe mitral regurgitation. AS: moderate or severe aortic stenosis. CLL: chronic lymphocytic leukemia. SLL: small lymphocytic lymphoma.

Table 2: Echocardiographic Measures in Patients on Ibrutinib with and without Atrial Fibrillation

	No Atrial Fibrillation (n = 44) *Mean Value ± SD, (n)*	**Atrial Fibrillation (n = 22)** *Mean Value ± SD, (n)*	**P-value**
RA Pressure	3.9 ± 2.5 (32)	4.2 ± 3.3 (19)	0.65
RV Size	3.3 ± 0.6 (43)	3.6 ± 0.8 (22)	0.08
RV Frac Area Change	49.9 ± 9.6 (42)	48.7 ± 10.7 (22)	0.65
RVSP	28.7 ± 9.8 (20)	30.8 ± 10.7 (16)	0.54
TAPSE	2.3 ± 0.5 (35)	2.3 ± 0.4 (18)	0.55
TR Vmax	246.2 ± 48.1 (22)	246.6 ± 52.7 (17)	0.98
Tricuspid S'	8.8 ± 1.8 (32)	8.2 ± 2.2 (17)	0.37
LAVI	27.1 ± 9.7 (44)	32.2 ± 12.0 (22)	0.07
E Velocity	79.9 ± 22.8 (35)	78.6 ± 25.3 (18)	0.85

	No Atrial Fibrillation (n = 44) *Mean Value ± SD, (n)*	**Atrial Fibrillation (n = 22)** *Mean Value ± SD, (n)*	**P-value**
A Velocity	74.9 ± 23.5 (35)	80.9 ± 30.3 (18)	0.43
E'm	7.7 ± 2.5 (32)	6.9 ± 2.7 (16)	0.29
E'l	9.6 ± 3.1 (34)	8.2 ± 2.9 (16)	0.15
E/e'	9.3 ± 3.1 (34)	11.5 ± 4.0 (16)	**0.04**
E decel time	202.1 ± 59.1 (33)	233.9 ± 75.0 (17)	0.11
LVEF	61.7 ± 8.0 (44)	62.7 ± 8.0 (22)	0.63
LV GLS	-19.4 ± 4.2 (42)	-18.6 ± 4.0 (21)	0.48

Among various baseline echocardiographic factors, E/e' was significantly higher for patients who developed IRAF. RA: right atrial. RV: right ventricular. Frac Area Change: fractional area change. RVSP: right ventricular systolic pressure. TAPSE: tricuspid annular plane systolic excursion. TR Vmax: tricuspid regurgitation maximal velocity. Tricuspid S': tricuspid annular peak systolic velocity. LAVI: left atrial volume indexed. E decel time: E deceleration time. LVEF: left ventricular ejection fraction. LV GLS: left ventricular global longitudinal strain.

Table 3: Left Atrial Strain Measures in Patients on Ibrutinib with and without Atrial Fibrillation

	No Atrial Fibrillation (n = 44) *Mean Value ± SD, (n)*	**Atrial Fibrillation (n = 22)** *Mean Value ± SD, (n)*	**P-value**
Peak Atrial Longitudinal Strain			
4 Chamber	35.9 ± 9.6 (38)	28.7 ± 10.3 (22)	**0.01**
2 Chamber	37.5 ± 9.2 (35)	30.8 ± 6.6 (20)	**0.01**
Mean	36.3 ± 8.7 (40)	30.3 ± 8.4 (22)	**0.01**
Peak Atrial Contraction Strain			
4 Chamber	17.4 ± 5.8 (29)	14.6 ± 5.3 (17)	0.11
2 Chamber	19.7 ± 5.5 (31)	16.5 ± 5.2 (19)	**0.05**
Mean	18.2 ± 5.3 (36)	15.6 ± 4.5 (21)	0.06
Conduit Strain	18.3 ± 6.3 (36)	14.9 ± 7.1 (21)	0.07

Peak atrial longitudinal strain (PALS) was evaluated in apical 4-chamber and apical 2-chamber views, and values were averaged to obtain the mean PALS. Similarly, peak atrial contraction strain (PACS) was evaluated in apical 4-chamber and 2-chamber views, with values averaged to determine mean PACS. Conduit strain was calculated as the difference between PALS and PACS. All values of PALS were significantly lower among patients who developed IRAF as compared to those who didn't. PACS and conduit strain were lower for patients who developed IRAF, though this did not reach statistical significance.

Table 4: Multivariate Regression Modeling for Factors Associated with Ibrutinib-Related Atrial Fibrillation

Variable 1	**Variable 2**	**Variable 1 p-value**	**Variable 2 p-value**
Age	Ibrutinib Dose	**0.004**	0.05
	E/e'	**0.003**	0.32

Variable 1	Variable 2	Variable 1 p-value	Variable 2 p-value
	PALS	**0.02**	0.07
	PACS	**0.002**	**0.04**
	Conduit Strain	**0.01**	0.46
PALS	Ibrutinib Dose	**0.01**	0.05
	E/e'	**0.004**	0.059
	PACS	0.30	0.79
	Conduit Strain	0.09	0.73
PACS	Ibrutinib Dose	**0.04**	0.11
	E/e'	**0.01**	**0.03**
	Conduit Strain	0.09	0.11

On multivariate regression modeling, age was significantly associated with IRAF when examined in pairs with ibrutinib dose, E/e', PALS, PACS and conduit strain. PALS was significantly associated with IRAF when evaluated in pairs with ibrutinib dose and E/e', but not with age. PACS was significantly associated with IRAF when evaluated in pairs with ibrutinib dose, E/e' and with age, suggesting an age-independent association of PACS and IRAF. PALS: peak atrial longitudinal strain; PACS: peak atrial contraction strain.

Figures

Figure 1: Left Atrial Strain on Echocardiography in Patients on Ibrutinib with and without Atrial Fibrillation.

A) Apical 2-chamber echocardiographic window with an LA strain contour for an adult male on ibrutinib therapy, who did not develop IRAF. B) LA strain tracing of the patient in panel A) demonstrating preserved PALS and PACS. Values represent population mean PALS and PACS with standard deviation and the number of patients on ibrutinib who did not develop IRAF. C) Apical 4-chamber echocardiographic window with an LA strain contour for an adult male on ibrutinib who developed IRAF. D) LA strain tracing of the patient in panel C) demonstrating decreased PALS and PACS. Mean values and standard deviation represent all patients on ibrutinib who developed AF. Notably, LA strain tracing demonstrates a loss of well-defined contractile function.