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Review Article

Cardiovascular Clinical Implications of Heart Rate Variability

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Abstract

Heart rate variability (HRV) is one of the promising emerging noninvasive modalities that are extensively used nowadays in research and risk stratification of several diseases. Reduced HRV has been linked to several cardiovascular risk factors such as hypertension (HTN) and diabetes mellitus (DM) also; it has been linked and used for years now in the risk stratification of congestive heart failure, coronary artery disease (CAD), and acute myocardial infarction (AMI). Controversial data are present about the effect of coronary artery bypass graft (CABG) on HRV and the use of HRV for risk stratification in post-CABG patients while percutaneous coronary intervention was linked to a dramatic improvement in HRV and improved survival of CAD patients. Although experimental data are present correlating reduced HRV with increased risk for cardiovascular morbidity and mortality, extensive research is required for further implementation in daily clinical use. In this review, we will discuss the current cardiovascular clinical implications and highlight the limitations of usage and future perspective of HRV.

Keywords: Acute myocardial infarction, autonomic nervous system, coronary artery disease, diabetes mellitus, heart rate variability, hypertension, percutaneous coronary intervention, risk stratification

Introduction

Heart rate variability (HRV) is the spontaneous fluctuations in the normal sinus rhythm; it can be measured as the standard or the average deviation from the mean R-R intervals of all cardiac cycle length (R-R intervals for normal sinus beats) over a given period.[1,2]

HRV is considered a reflection of natural sympathovagal balance on the heart or the normal activity of the autonomic nervous system (ANS).

Several methods have been proposed by the Task Force of the European Society of Cardiology (ESC) and the North American Society of Pacing and Electrophysiology (NASPE) to define and to establish the standards of measurement, physiological interpretation, and clinical use of HRV.[3] Time domain indices, nonlinear geometric measures, and frequency domain indices are considered the standard clinically used parameters.[4] The analysis of HRV data should meet the defined standards of measurement by the Task Force of ESC and NASPE either through the short-term recordings of 5 min made under physiologically stable conditions and/or long 24-h recordings (Holters).[3] Over the past years, HRV has been correlated with most cardiovascular diseases and risk factors.[2]

Clinical perspective:

To review the current clinical trials that linked heart rate variability to different cardiovascular risk factors and diseases and to determine usage limitations and future prospectives of heart rate variability as a noninvasive diagnostic modality in risk stratification of several cardiovascular diseases.

Clinical Implications of Heart Rate Variability

Hypertension

One of the most important risk factors for coronary artery disease (CAD) is hypertension (HTN). Numerous studies

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have documented the association between cardiac autonomic dysfunction and HTN.[5]

Huikuri *et al*. studied the correlation between HRV and long-standing systemic HTN comparing patients with long-standing HTN with the age-matched normotensive population. The data showed that long-standing HTN results in reduced overall HRV suggesting that low HRV may contribute to increased cardiac mortality in patients with long-standing HTN.[6]

Liao *et al*. examined the association between 2 min of supine HRV and HTN in a random sample derived from the biracial Atherosclerosis Risk in Communities (ARIC) study with a 3-year follow-up. The results suggested a positive correlation between decreased HRV and HTN and furthermore suggest that decreased HRV was associated with increased risk for HTN.[7]

Singh *et al*. conducted a study aiming to compare the measures of HRV between hypertensive and normotensive subjects and to examine the role of HRV as a predictor of new-onset HTN using data derived from the Framingham Heart Study (FHS). HRV was significantly lower in hypertensive men and women while among normotensive men, lower HRV was associated with greater risk of developing HTN. These findings are consistent with the hypothesis that autonomic dysregulation is present in the early stages of HTN.[8]

Diabetes mellitus

Diabetes mellitus (DM) is another important risk factor for CAD has also been linked to decreased HRV. Autonomic neuropathy is a common complication of DM, and the early subclinical detection of autonomic dysfunction may be important for the risk stratification and subsequent management of diabetics.[5]

In the first study to examine the relationship between HRV as an indicator of ANS and DM, Liao *et al*. computed high-frequency power (HF) as index of vagal tone from 2-min recordings of a sample derived from the ARIC and found that DM was associated with a lower HRV than age, race, and gender-matched nondiabetics also, prediabetics were associated with a reduce HRV suggesting that reduced vagal tone may be involved in the pathogenesis of DM.[9]

Singh *et al*. examined the relationship between HRV and blood glucose levels from data derived from the FHS. HRV indices were significantly reduced in diabetics and those with impaired fasting glucose compared to those with normal fasting glucose levels.[10]

Heart failure

The ANS regulation plays an important role in the progression of congestive heart failure (CHF).[11] It may affect the cardiovascular system in heart failure in several ways including downregulating ß-adrenergic receptors, exerting direct toxic effects on the myocardium, and contributing to myocardial remodeling and life-threatening arrhythmias. In this sense, CHF patients are a high-risk group for death.[4]

Ventricular tachycardias often occur in patients with compromised left ventricular ejection fraction (LVEF) and up to 80% of patients may die suddenly with an average 60% survival at 4 years.[4]

Sympathetic activation and reduced vagal tone are usually reflected by a significant increase in low-frequency power (LF) and decrease in HF component and this sufficiently intact sympathetic activation at less advanced stages of CHF reflected by increased LF contribute to arrhythmogenesis and sudden death.[12]

In the advanced stages of heart failure, there is a loss of rhythmicity in the LF and HF components. A particular finding is the highly reduced or even undetectable LF in spite of the high levels of sympathetic activation. This behavior of the LF component suggests that the integrity of the sympathetic innervation becomes defective with the progression of CHF.[12] The highly reduced LF power in the advanced stages of CHF may be secondary to abnormalities in central autonomic regulation and impairment of ß-adrenergic receptor sensitivity.[10,13]

Patients in very advanced stages of the disease behave as if they had cardiac denervation and loss of neural modulation of cardiac rate, resembling patients with recently transplanted hearts.[14] HRV may be used in patients with CHF as a marker for the prediction of mortality due to progressive LV dysfunction and to sudden cardiac death.[15-19]

Coronary artery disease

Autonomic dysfunction in the form of enhanced sympathetic tone and reduced vagal tone and has been suggested in CAD in the early reports.[20-22]

Wennerblom *et al*. investigated the correlation between uncomplicated CAD and reduced HRV using frequency domain measures and proved that uncomplicated CAD in patients without previous acute myocardial infarction (AMI) or any other diseases were associated with reduced HF and LF HRV as a marker of reduced vagal tone.[23]

Feng *et al*. studied the alteration of HRV time domain measures depending on the characteristics of coronary lesions in stable angina pectoris patients summarizing that compared with a control group, standard deviation of all R-R intervals measured in milliseconds (SDNN) in one-vessel, SDNN, standard deviation of the averages of R-R intervals in all 5-min segments of the entire recording measured in ms (SDANN) in two-vessel disease and in three-vessel disease were lower and compared with two-vessel disease, SDNN, SDANN lower in three-vessel disease. Compared with right CAD, SDNN and SDANN in the left CAD group were lower, while compared with lesions in left circumflex, SDNN in lesions in the left anterior descending artery is lower.[24]

Li *et al*. correlated HRV measures with angiographic CAD in patients with stable angina, independently from other traditional risk factors, comorbidities, medications, or Framingham risk. In addition proved that in patients with high risk of CAD, HRV was even more predictive. Measures of HRV may provide specific advantages in clinical practice

to improve the risk reclassification of the angiographic CAD.[25]

Kotecha *et al*. highlighted that low HRV particularly LF power in a 5-min analysis of HRV is strongly predictive of angiographic CAD regardless of other comorbidities and is clinically useful as an independent risk predictor in obstructive CAD patients with sinus rhythm.[26]

Myocardial infarction

The significance of HRV and its prognostic valve in AMI survivors has been extensively studied over the years. Wolff *et al*. were the first to assume that HRV measured on the admission of AMI patients can be a predictor of mortality, HRV was measured in 60-s electrocardiogram strips. Patients with a decreased HRV tended to be older, more likely to have an anterior infarct, and more likely to have heart failure. The study concluded that decreased HRV can be used as an independent predictor of adverse outcome and may predict long-term risk after AMI.[27]

Kleiger *et al*. described the first study that clearly documents the independent and long-term predictive valve of HRV analysis of survivors of AMI through the multicenter postinfarction program (MPIP). 24-h Holter of AMI survivors was evaluated; HRV was proven to be the strongest predictor of mortality.[28]

Lombardi *et al*. studied the sympathovagal interaction in AMI patients using analysis of spectral components of HRV over 1 year. At 2 weeks after AMI, the LF component was significantly increased, the HF component was significantly reduced compared to age-matched control subjects. While at 6 and 12 months after AMI, a progressive decrease in the LF and increase in the HF components was observed.[29]

Cripps *et al*. conducted a study measuring HRV index in 24-h Holter of AMI survivors aiming to assess this novel measurement of HRV and to relate the prognostic significance of decreased HRV using to other well-recognized prognostic variables such as late potentials, reduced LVEF, in-hospital complication, and KILLIP class.[30] Other studies (including a reanalysis of MPIP) have shown that spectral measures of HRV are reduced in survivors of AMI and that decreased values were associated with an increased risk of all-cause mortality.[31]

The autonomic tone and reflexes after myocardial infarction trial was a multicenter observational study performed about 10 years after MPIP. The data confirmed that reduced SDNN was associated with an increased mortality during 21 months of follow-up. Furthermore, the combination of low SDNN and LVEF <35% carried a higher risk of mortality.[32] HRV is decreased early after AMI and begins to recover within a few weeks. It is maximally but not fully recovered by 6–12 months after AMI.[33,34] The assessment of HRV at both the early stage of MI (2–3 days after AMI)[35] and pre-discharge from the hospital (1–3 weeks after acute MI) offers important prognostic information. HRV measured 12-month after AMI also predicts further mortality.[34]

Effect of Revascularization on Heart Rate Variability

Heart rate variability and coronary artery bypass graft

Previous studies have shown decreased HRV after coronary artery bypass graft (CABG) even more significantly than in patients with AMI[36] with a gradual recovery in a few months following the operation.[37,38] Possible reasons for a decreased HRV after CABG is a combination of surgical manipulation on the heart and other anatomic structures around the heart, anesthesiological procedures, duration of cardioplegia also, extracorporeal circulation, etc.[39-41] According to some reports, unlike decreased HRV in patients after AMI, decreased post-operative HRV do not have any significant prognostic valve in CABG patients.[42,43] Contrary to those previous reports, recent studies showed that the CABG patients with post-operative decreased HRV have a higher mortality rate than patients with normal HRV with furthermore research is required for further assessment of the prognostic impact of HRV in CABG patients.[44]

Heart rate variability and percutaneous coronary intervention

Patients with CAD and exercise-induced angina pectoris have a state of sympathetic hyperactivity,[45] and it seems that the myocardial ischemia is the trigger of this sympathetic hyperactivity; hence, theoretically, revascularization by percutaneous coronary intervention (PCI) can restore the normal autonomic balance.[46]

Sedziwy *et al*. studied HRV time domains before PCI and during a 1-year follow-up using serial 24-h Holter monitoring in all patients (before PCI, 14 days, 3, 6, and 12 months after PCI). A significant increase of HRV parameters was noted with statistically significant increase of HRV parameters occurred during the first 3-month follow-up while the results of the next serial recordings (6 and 12 months after PCI) demonstrated no additional changes in HRV values; however, they were still significantly higher than before procedure concluding that successful revascularization using PCI leads to an improvement in the autonomic balance of HRV.[47] Aydinlar *et al*. investigated the effect of PCI on QT dispersion and HRV time and frequency domain parameters and concluded that HRV parameters such as HF component, the square root of the mean of the sum of the squares of differences between adjacent NN intervals measured in ms (rMSSD) and SDNN were significantly increased while LF, LF/HF were significantly reduced. In addition, QT dispersion was significantly decreased with a negative correlation to LF component and LF/HF ratio.[48] Abrootan *et al*. studied the changes in HRV parameters after elective PCI in patients with stable angina pectoris. Short-term HRV measurement using time domain parameters was done before PCI and 24-h post-PCI. The data indicated that among different time-domain HRV parameters, only SDNN increased significantly, with a considerable yet statistically insignificant increase in rMSSD after PCI.[46]

Limitations and future prospectives of heart rate variability

In spite of the large number of the currently published experimental and clinical trials concerned with HRV measurements and several clinical implications. Yet still, the use of HRV is limited to research and not routinely used in daily clinical practice.[49] Several reasons have been proposed to explain this issue: First, the pathophysiological mechanism of HRV confirming the direct relation between mortality and reduced HRV is still not fully understood. Second, the clinical application of HRV assessment is limited by the lack of standard methods due to variations of the parameters according to gender, age, drug interferences, and concomitant diseases. Third, so far, there is no consensus about the most accurate HRV parameter for clinical use. Fourth, the sensitivity, specificity, and positive predictive accuracy of HRV are still limited. Particularly, its positive predictive accuracy is modest, ranging from 14% to 40%. Yet, it has a higher negative predictive value ranging from 77% to 98%. Fifth, conflicting data[50] have been noted regarding HRV measured after MI, suggesting that it may be insufficient by itself for proper risk stratification in high-risk patients. A combination of HRV and other risk stratification methods including LVEF, nonsustained ventricular tachycardia, and baroreceptor sensitivity may improve the overall predictive accuracy.[32,51,52] and finally, because HRV measurement depends on R-R interval variations, so the measurement is restricted to sinus rhythm patients and to those with a low number of ectopic beats. Due to this issue, some high-risk patients are excluded from HRV analysis due to frequent ectopy or atrial arrhythmias. Approximately 20–30% of high-risk post-AMI patients and up to 15–30% CHF patients are excluded for HRV analysis due to frequent ectopic beats or more commonly atrial fibrillation that is observed in up to 15%–30% of patients with CHF.[4]

Conclusion

HRV is one of the most promising methods for detection and quantification of autonomic dysfunction. Further research is required to define its effectiveness in clinical usage and to validate its usefulness in risk stratification in cardiovascular risk factors and diseases.

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Original Article

Knowledge Regarding the Signs, Symptoms, and Risk Factors Associated with Stroke in Medical and Nonmedical Personnel

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Abstract

Introduction: Stroke was the second-leading global cause of death accounting for 11.8% of total deaths worldwide and a leading cause of disability. Stroke was the leading cause of death in Indonesia accounting for 21.1% of them. Knowledge is essential for the prevention of stroke and minimizing delay in receiving proper treatment. **Methods:** This was a cross-sectional observational study using a questionnaire consisting of questions about signs, symptoms, and risk factors for stroke in the Indonesian Language with a minimal amount of technical jargon. There were 113 respondents, 49 has a medical background (11 was medical doctors) and 64 was from a nonmedical background. **Results:** Majority of the nonmedical personnel knew that hemiparesis is a symptom of stroke, but only a third knew that hemihypesthesia is one of the symptoms. Approximately half knew that dysarthria and uneven face is a symptom of stroke. Only a few knew that sudden loss of vision is a symptom of stroke. Hypertension and hypercholesterolemia were the two most popular risk factors among nonmedical personnel, other risk factors were only known to <40% of the respondents. After comparing the results between medical and nonmedical personnel, medical personnel was more confident about their knowledge ($P < 0.001$). The difference was also statistically significant in hemihypesthesia ($P = 0.029$) and sudden loss of vision ($P = 0.032$). The difference was statistically significant when assessing several risk factors such as arrhythmia ($P = 0.004$), smoking ($P = 0.004$), hypertension ($P = 0.001$), diabetes ($P < 0.001$), and atrial fibrillation ($P < 0.001$). Disappointingly, both groups performed poorly in recognizing menopause as a risk factor. **Conclusion:** The knowledge about the symptoms and signs of stroke other than hemiparesis was poor in nonmedical personnel. Medical personnel was only slightly better than nonmedical personnel. This is a wake-up call to emphasize the importance of stroke, its prevention and early recognition.

Keywords: General population, knowledge, risk factors, stroke, symptoms

Introduction

Data showed that in 2013, stroke was the second-leading global cause of death behind ischemic heart disease, accounting for 11.8% of total deaths worldwide and a leading cause of disability.[1,2] The magnitude of the problem is even greater in Indonesia, being the leading cause of death accounting for 21.1% of them, surpassing the ischemic heart disease.[3] Knowing the risk factors involved in stroke is essential to reduce the incidence. For the general population, knowing risk factors involved in stroke may help the individuals to be more aware and actively preventing the disease in themselves and other people related to them. For medical personnel, astute knowledge is important to help them to screen, advise, and address the risk factors in patients. For nonmedical personnel, the insight of sign and symptoms of stroke is essential to shorten the period between onset of symptoms and medical care. There was a saying that in stroke, "time is the brain," and the prognosis may differ largely if the patient presented/diagnosed early. Ischemic

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stroke patients might be able to get reperfusion treatment if they presented within the requisite timeframe.[4] An individual educated in such knowledge will be more likely to recognize a stroke and helps themselves or other people to get early medical attention. Medical personnel with good knowledge of stroke will be less likely to miss the diagnosis even when the symptom was atypical. Delay in treatment resulting from poor knowledge regarding symptoms and signs of stroke may lead to a poorer prognosis.[5] The aim of our study is to assess the knowledge regarding the symptoms and risk factors of stroke from both medical and nonmedical personnel, then compared the knowledge between them.

Methods

Setting

This study was conducted in January 2018 in Jakarta, Indonesia.

Study design

This was a cross-sectional observational study using a questionnaire. We assessed the knowledge about signs, symptoms, and risk factors for stroke through a questionnaire in the Indonesian Language with a minimal amount of technical jargon. The questionnaire consists of the questions with multiple choice answer and checklists. The sample was taken randomly consenting participants from both medical and nonmedical personnel in Jakarta, Indonesia.

Statistical analysis

The analysis was performed to assess the difference in knowledge between medical and nonmedical personnel; subsequent analysis was performed between doctors and other medical personnel. There were 113 respondents, 49 has a medical background (11 were medical doctors) and 64 was from a nonmedical background. Information from the questionnaire was coded and entered into IBM Statistical Package for Social Sciences (SPSS) Statistics for Windows, (Version 24.0, Armonk, NY: IBM Corp., USA). The difference in knowledge between medical and nonmedical personnel; doctors, and other medical personnel were compared using the Chi-square test. The mean difference (continuous variable) was analyzed using *t*-test.

Results

In a question regarding nonmedical personnel subject's knowledge about stroke according to him/herself, 37 (57.8%) respondents said they knew well about it. Fifty-five respondents (85.9%) knew about hemiparesis. Twenty-one respondents (32.8%) knew about hemihypesthesia. Thirty-seven respondents (57.8%) knew about the uneven face. Twenty-nine respondents (45.4%) knew about dysarthria. Only seven respondents (10.9%) knew that sudden loss of vision is a symptom of stroke. Mean for knowing some risk factors out of 5 was 2.33. Twenty-five respondents (39.1%) knew that older people are at higher risk for stroke. Eight respondents (12.5%) knew that gender is a risk factor. Seventeen respondents (26.6%) knew that arrhythmia is a risk factor. Eleven respondents (17.2%) knew that family history plays a part. 18 respondents (28.1%) knew that smoking increased the risk of stroke. 42 respondents (65.6%) knew that hypercholesterolemia was associated with stroke. As for hypertension and diabetes, 50 respondents (78.1%) and 10 respondents (15.6%) knew that they were risk factors for stroke. Nobody knows that menopause is a risk factor for stroke. Mean for knowing some risk factors out of 9 was 2.77.

In a question regarding a subject's knowledge about stroke according to him/herself, medical personnel were more confident about their knowledge ($P < 0.001$) [Table 1]. The difference was also statistically significant in hemihypesthesia ($P = 0.029$) and sudden loss of vision ($P = 0.032$). The difference was not statistically significant when assessing hemiparesis, dysarthria, and uneven face ($P = 0.742$, $P = 0.055$, and $P = 0.078$). The difference was significant when assessing several risk factors such as arrhythmia ($P = 0.004$), smoking ($P = 0.004$), hypertension ($P = 0.001$), diabetes ($P < 0.001$), and atrial fibrillation ($P < 0.001$). Disappointingly, both performed poorly in recognizing menopause as a risk factor (0 in nonmedical vs. 2 in medical, $P = 0.362$). The difference was not significant in knowing that age ($P = 0.197$), gender ($P = 0.16$), and cholesterol ($P = 0.49$) as a risk factor. The difference in knowing symptoms (out of 5) and risk factors (out of 9) are 0.815 ($P = 0.004$) and 1.76 ($P < 0.001$). The difference in knowledge between doctor and other medical personnel was slim, with only menopause the only differing factor ($P = 0.047$) [Table 2].

Discussion

Among the nonmedical personnel, hemiparesis was the most well-known symptom of stroke. Hemiparesis is one the most familiar symptom of stroke among the general population, be it on films, movies, or regular conversation. Half knew that uneven face is a sign of stroke; it is one of the components of the acronym "FAST" which is often promoted in Western countries. It is less frequently heard in Indonesia. The acronym "FAST" in the Indonesian language should be broadcasted more frequently for a public audience to see. Fewer knew that hemihypesthesia is a symptom of stroke, possibly because the symptom is less alarming than hemiparesis, nonmedical personnel, especially the less educated individual, may mistake it for "fatigue." Only a small fraction knew that sudden loss of vision is a symptom of stroke, this should be more emphasized since it might be an episode of transient ischemic attack which further increases the risk of subsequent stroke.[6] Most did not know that arrhythmia (atrial fibrillation) is a risk factor for stroke, atrial fibrillation itself was mostly unknown among nonmedical personnel. However, there was atrial fibrillation campaign in recent years, and it is hoped that more will be aware of atrial fibrillation. Hypertension was the most popular risk factor for stroke in our sample, but only

Table 1: The knowledge regarding sign, symptoms, and risk factors of stroke among medical and nonmedical personnel

	Medical personnel		Total	Percentage sample	*P*
	No	Yes			
Know about stroke?					
Yes	37	47	84	74.3	<0.001
Not fully understand	27	2	29	25.7	
Stroke is the highest cause of disability					
Yes	46	42	88	77.9	0.127
No	18	7	25	22.1	
Knowledge about stroke (mean/median)					
Hemiparesis/plegia?					
Yes	55	44	99	87.6	0.742
No	9	5	14	12.4	
Hemihypesthesia?					
Yes	21	27	48	42.5	0.029
No	43	22	65	57.5	
Uneven face					
Yes	37	37	74	65.5	0.078
No	27	12	39	34.5	
Dysarthria					
Yes	29	32	61	54.0	0.055
No	35	17	52	46.0	
Sudden loss of vision					
Yes	7	14	21	18.6	0.032
No	57	35	92	81.4	
Risk factors for stroke (mean/median)					
Age					
Yes	25	26	51	45.1	0.197
No	39	23	62	54.9	
Gender					
Yes	8	12	20	17.7	0.16
No	56	37	93	82.3	
Heart rhythm					
Yes	17	27	44	38.9	0.004
No	47	22	69	61.1	
Family history					
Yes	11	17	28	24.8	0.055
No	53	32	85	75.2	
Smoking					
Yes	18	28	46	40.7	0.004
No	46	21	67	59.3	
Cholesterol					
Yes	42	36	78	69.0	0.491
No	22	13	35	31.0	
Hypertension					
Yes	50	49	99	87.6	0.001
No	14	0	14	12.4	
Diabetes					
Yes	10	26	36	31.9	<0.001
No	54	23	77	68.1	
Menopause					
Yes	0	2	2	1.8	0.362
No	64	47	111	98.2	
Atrial fibrillation					
Yes	20	37	57	50.4	<0.001
No	44	12	56	49.6	

Table 2: The knowledge regarding sign, symptoms, and risk factors of stroke among doctors and other medical personnel

	Medical personnel		Total	Percentage sample	*P*
	No	Yes			
Know about stroke?					
Yes	11	36	47	41.6	<0.001
Not fully understand	0	2	2	1.8	
Stroke is the highest cause of disability					
Yes	11	31	42	37.2	0.33
No	0	7	7	6.2	
Knowledge about stroke (mean/median)					
Hemiparesis/plegia?					
Yes	11	33	44	38.9	0.574
No	0	5	5	4.4	
Hemihypesthesia?					
Yes	7	20	27	23.9	0.732
No	4	18	22	19.5	
Uneven face					
Yes	9	28	37	32.7	0.708
No	2	10	12	10.6	
Dysarthria					
Yes	9	23	32	28.3	0.287
No	2	15	17	15.0	
Sudden loss of vision					
Yes	3	11	14	12.4	0.914
No	8	27	35	31.0	
Risk factors for stroke (mean/median)					
Age					
Yes	7	19	26	23.0	0.649
No	4	19	23	20.4	
Gender					
Yes	5	7	12	10.6	0.108
No	6	31	37	32.7	
Heart rhythm					
Yes	8	19	27	23.9	0.303
No	3	19	22	19.5	
Family history					
Yes	6	11	17	15.0	0.156
No	5	27	32	28.3	
Smoking					
Yes	9	19	28	24.8	0.087
No	2	19	21	18.6	
Cholesterol					
Yes	10	26	36	31.9	0.256
No	1	12	13	11.5	
Hypertension					
Yes	11	38	49	43.4	-
No	0	0	0	0.0	
Diabetes					
Yes	9	17	26	23.0	0.068
No	2	21	23	20.4	
Menopause					
Yes	2	0	2	1.8	0.047
No	9	38	47	41.6	
Atrial fibrillation					
Yes	10	27	37	32.7	0.252
No	1	11	12	10.6	

minority knows that diabetes and smoking are an important risk factor for stroke.

Almost all of the medical personnel knew that hemiparesis is the presenting symptom of stroke, the knowledge was excellent in both medical and nonmedical personnel. Only a small fraction of medical personnel knew that sudden loss of vision is a sign and symptom of stroke, although they perform reasonably well when compared to nonmedical personnel, it is still a disappointing result. Medical personnel was better compared to nonmedical personnel in identifying atrial fibrillation, diabetes, hypertension, and smoking as risk factors. Despite a better result, only 26 out of 49 correctly identifies diabetes as a risk factor. Diabetes is one of the major risk factors for stroke, and all of the medical personnel should be able to identify it correctly.[7] However, the result is most disappointing in menopause, as only 2 out of 49 medical personnel know and did not perform better compared to nonmedical personnel. Subsequent analysis found that only menopause was significant for the difference in knowledge between doctors and other medical personnel, which means that the knowledge about stroke is still poor.

Conclusion

The knowledge regarding the symptoms and signs of stroke other than hemiparesis was poor, especially regarding the sudden loss of vision. The most popular risk factors are hypertension and hypercholesterolemia. However, respondents lacked the knowledge about other risk factors.

The result that the medical personnel can only recognize symptoms slightly better than the nonmedical personnel was slightly disappointing, and both performed relatively poor in answering questions. This is a wake-up call to emphasize the importance of stroke, its prevention and early recognition.

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Conflicts of interest

There are no conflicts of interest.

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Original Article

The Relationship between Epicardial Fat Tissue Thickness and Red Blood Cell Distribution Width in Patients with Type 2 Diabetes Mellitus

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Abstract

Aim: Red blood cell distribution width (RDW) and epicardial fat tissue (EFT) are considered as a novel risk factor for cardiovascular disease. However, their relationship in patients with type II diabetes mellitus (DM) has never investigated before. **Materials and Methods:** Our study was a single-center prospective study which included 159 diabetic patients and 153 healthy controls. Two-dimensional and M-mode echocardiographic examination was performed using standard apical, parasternal, and subcostal views in all the study participants. **Results:** EFT thickness and RDW were found to be significantly higher in diabetic patients compared to controls (4.3 ± 1.1 mm vs. 3.7 ± 1.0 mm $P = 0.001$ and 13.5 ± 0.7 vs. 13.2 ± 0.9 $P = 0.044$, respectively). EFT thickness and RDW were positively correlated. RDW value of 13.55 predicted EFT thickness >5 mm with a sensitivity of 61.7% and specificity of 58.8% (area under the curve [AUC]: 0.649 and $P = 0.001$). HgA1C value of >7 predicted EFT thickness ≥4.15 mm with a sensitivity of 60.7% and specificity of 60.4% (AUC: 0.651 and $P < 0.001$). No correlation found between RDW and HgA1C (AUC: 0.554 and *P*: 0.169). **Conclusion:** EFT thickness increased in diabetic patients, independent of age, gender, waist circumference, body mass index, and it was correlated with RDW and HgA1C.

Keywords: Epicardial fat tissue thickness, red blood cell distribution width, type 2 diabetes mellitus

Introduction

Epicardial fat tissue (EFT) is a small yet functional visceral fat depot which has different properties from other fat depots. Due to its paracrine and vasocrine activities, it plays a prominent role in inflammatory and atherosclerotic processes.[1,2] Previous studies have shown that EAT thickness is higher in diabetic patients.[3]

Red blood cell distribution width (RDW) which is used for measuring the size heterogeneity of the erythrocytes could be obtained readily from full blood count. Greater heterogeneity of cell size yields larger RDW. It is identified as a reflection of chronic inflammation and evidence suggests that higher levels are closely related to the elevated high-sensitivity-C-reactive protein and erythrocyte sedimentation rate levels.[4] Increased RDW level independently predict the poorer outcome in ischemic heart disease, congestive heart failure, peripheral artery disease, and in-stent restenosis.[5]

Diabetes mellitus (DM) is a serious disease that is associated with important complications and its incidence increasing rapidly. It affects both macro- and microcirculation and has serious long-term complications. Hyperglycemia reduces

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the lifespan of erythrocytes leading to volume changes.[6] Among patients with DM, increased RDW levels indicate poor glycemic control.[7,8] In our study, we have attempted to investigate the possible differences in variables such as RDW and EFT thickness between diabetic and healthy patients and to assess the correlation (if any) between those parameters.

Materials and Methods

One hundred and fifty-nine type II diabetic patients and 153 healthy counterparts were enrolled in this single-center, prospective study. The study was approved by Kafkas University Medical Faculty ethical commitee (ethical committee number: 80576354-050-99, approval date: 14/03/2008). Clinical and demographic variables, medical history, and concomitant medications of the patients were measured at baseline. Data regarding diabetes duration and medications taken by the diabetic patients were also recorded. Diagnosis of type II DM was made according to the American Diabetes Association criteria.[9] Patients with anemia (hemoglobin <12 g/dl), chronic renal failure, obesity, congestive heart failure, active infection, chronic inflammatory diseases, malignancy, history of coronary artery bypass graft or percutaneous intervention, previous myocardial infarction, and stable or unstable angina were excluded from the study.

Fasting blood samples were drawn from the antecubital vein with the patient resting in the supine position. All specimens were analyzed on the same day in the biochemistry laboratory. Biochemical analysis was performed by Cobas c311 (Roche Diagnostics, Germany) and the following parameters were measured: fasting glucose, hemoglobin A1c, C-reactive protein, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), and low-density lipoprotein cholesterol (LDL-C). The blood parameters of all participants including hemoglobin, RDW, and platelet count, were studied by Cell-Dyn 3700 (Abbott Laboratories, Abbott Park, Illinois, USA).

All patients had 12-lead resting electrocardiogram in the supine position and had complete echocardiographic examination (Vivid 3 pro, GE Vingmed Ultrasound AS, Horten, Norway). The same cardiologist who was blinded to the clinic of the patients was performed the echocardiographic examination based on the recommendations of the American Society of Echocardiography.[10] Simpson rule was used for calculating the left ventricular ejection fraction (LVEF). EFT was appeared as the hyperechoic space in the anterior face of the right ventricle, and its thickness was measured perpendicularly ahead of the right ventricular free wall, at the end-diastole from the parasternal long- and short-axis views.[11]

Continuous variables were presented as mean and standard deviation. Categorical variables were reported as percentages. Student's *t*-test was used to compare the parametric continuous variables. Nonparametric continuous variables and categorical variables were compared by Mann–Whitney U-test and Chi-square test, respectively. Pearson's correlation test was used to examine the correlation between the variables. For the cutoff values RDW and EFT, ROC curve analysis was used. All confidence intervals were 95%. $P < 0.05$ was regarded as statistically significant. All statistical analyses were performed using the SPSS program v. 15.0 (SPSS Inc., Chicago, IL, USA).

Results

The study sample consisted of 312 patients. Among 159 diabetic patients, 65 were male, 94 were female, and among 153 control patients, 67 were male and 86 were female. Clinical characteristics of the patients such as age, sex, smoking, body mass index (BMI), systolic blood pressure, and LVEF were similar between the two groups. All the patients were on sinus rhythm during the study entry. Diastolic blood pressure of the diabetic patients was significantly higher than the healthy participants [Table 1].

Diabetic patients had increased EFT thickness (4.3 ± 1.1 mm vs. 3.7 ± 1.0 mm $P = 0.001$), higher RDW values (13.5 ± 0.7 vs. 13.2 ± 0.7 $P = 0.001$), LDL-C, TG, and

Table 1: Baseline characteristics of the patients

	Diabetic group ($n=159$)	Control group ($n=153$)	*P*
Age (years)	51.9±7.6	51.4±6.5	0.061
Female, *n* (%)	94 (62.6)	86 (56.2)	0.343
Male, *n* (%)	65 (37.4)	67 (43.8)	0.343
LVEF (%)	64.3±8.2	65.4±7.4	0.86
Smokers, *n* (%)	43 (28.6)	42 (27.7)	0.831
BMI (kg/m^2)	28.5±1.3	28.4±1.2	0.062
SBP (mmHg)	130.3±10.3	126.3±11.4	0.08
DBP (mmHg)	77.0±7.7	73.5±8.1	0.018

BMI: Body mass index, DBP: Diastolic blood pressure, LVEF: Left ventricular ejection fraction, SBP: Systolic blood pressure

Table 2: Biochemical and hematological parameters of the patients

	Diabetic ($n=159$)	Nondiabetic ($n=153$)	*P*
TG (mg/dl)	149.7±13.1	139.9±13.2	<0.001
LDL-C (mg/dl)	143.5±14.8	128.2±16.0	<0.001
HDL-C (mg/dl)	43.4±5.5	44.6±6.1	0.051
WBC count (10^9/µl)	8.1±1.1	7.8±1.0	0.065
RDW (%)	13.5±0.7	13.2±0.7	0.001
Hemoglobin (g/l)	13.2±0.7	13.4±0.7	0.081
Platelet count (10^9/µl)	260.3±50.3	258.5±53.4	0.764
FPG (mg/dl)	106.5±18.6	86.3±10.9	<0.001
A1c (%)	7.3±0.8	4.9±1.0	<0.001
C-reactive protein (mg/l)	2.6±2.1	2.2±1.8	0.09
Creatinine (mg/dl)	0.91±0.24	0.87±0.21	0.09
EFT (mm)	4.3±1.1	3.7±1.0	0.001

Measuring units and reference ranges: WBC count: 4-11×10^9/µL, platelet count: 140-440×10^9/µL, RDW: 11%-14%. EFT: Epicardial fat thickness, FPG: Fasting plasma glucose; HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, WBC: White blood cell, RDW: Red cell distribution width, TG: Triglyceride

HgA1c levels compared to their healthy counterparts. Although HDL-C value was found to be higher in the control group, it did not carry statistical significance. The results of the serum biochemistry and hematological indices are shown in Table 2.

On correlation analysis, RDW and EFT (0.384, $P < 0.001$) were strongly positively correlated. RDW was also positively correlated with LDL-C, TG, and HgA1c levels and negatively correlated with HDL-C level. Parameters that are correlated with RDW are listed in Table 3. RDW value of 13.55 predicted EFT thickness >5 mm with a sensitivity of 61.7% and specificity of 58.8% (*P*: 0.001, Area under the curve [AUC]: 0.649, CI 95%: 0.564–0.733) [Figure 1]. HgA1C value of >7 predicted EFT thickness ≥4.15 mm with a sensitivity of 60.7% and specificity of 60.4% (AUC: 0.651 vs. $P < 0.001$) [Figure 2]. According to the power analysis, the strength to EFT in predicting the diabetic patients (alpha value = 0.05 and 95% confidence) was 99.9%.

Discussion

Our study showed that EFT thickness increased in diabetic patients, independent of age, gender, waist circumference, BMI, and it was correlated with RDW. As far as our best knowledge from the literature, our study is the first study showing a positive relation between EFT thickness and RDW in diabetic patients. EFT has both paracrine and vasocrine activities and secretes a range of chemokines such as tumor necrosis factor-α, interleukin-6, interleukin-1b, monocyte chemoattractant protein-1, angiotensin II, and resistin.[2,12,13] It has been suggested to influence atherosclerotic lesion progression, plaque vulnerability, and destabilization.[14] Echocardiographic- and computed tomography (CT)-derived measurements of the epicardial adipose tissue (EAT) thickness have been found to be in correlation with the fasting blood glucose levels.[15] Diabetic patients have increased EFT thickness as compared to nondiabetic participants, and it has a positive correlation with HbA1c levels.[16] Arpaci *et al*.[17] reported that prediabetic patients had higher EFT values which were directly correlated with the patients' BMI and waist circumference. Another study led by Altın *et al*.[18] investigated the relationship between fasting glucose levels and EFT and carotid intima-media thickness (CIMT) in prediabetic patients. In that study, prediabetic patients had higher EFT and CIMT, indicating that these two cardiovascular risk parameters could be used for risk stratification in that patient group. Studies have found positive relationship between EAT thickness and plasma level of insulin, retinol binding protein 4, and mRNA expression of resistin which are associated with insulin resistance.[19-21]

EFT might be a modifiable risk factor or a target to modify cardiovascular risk. EFT and CIMT values of the asymptomatic obese patients were shown to be decreased after significant weight loss.[22] Weight loss reverses the insulin resistance and decrease of EAT thickness in patients with metabolic syndrome.[19] Serial measurement of EFT during follow-up of the patients may give additional information about their cardiovascular risk profile.

RDW is an indicator of erythrocyte anisocytosis, can be easily calculated from complete blood count. It has been found to have prognostic value in several diseases, such as coronary artery disease, left ventricular systolic failure, cerebrovascular disease, and chronic obstructive pulmonary

Table 3: Parameters that are correlated with red cell distribution width

	r	*P*
EFT thickness (mm)	0.402	<0.001
HDL-C (mg/dl)	−0.235	0.003
LDL-C (mg/dl)	0.398	<0.001
TG (mg/dl)	0.134	0.05
WBC count (10^9/μl)	0.311	<0.001

EFT: Epicardial fat tissue, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, TG: Triglyceride, WBC: White blood cell

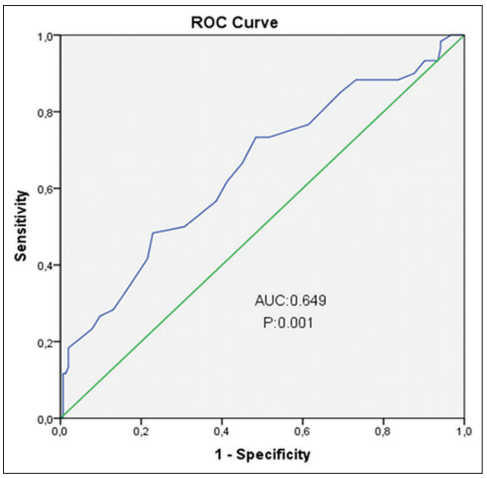


Figure 1: Receiver-operating characteristic curve analysis of red blood cell distribution width value to predict epicardial fat tissue ≥5 mm

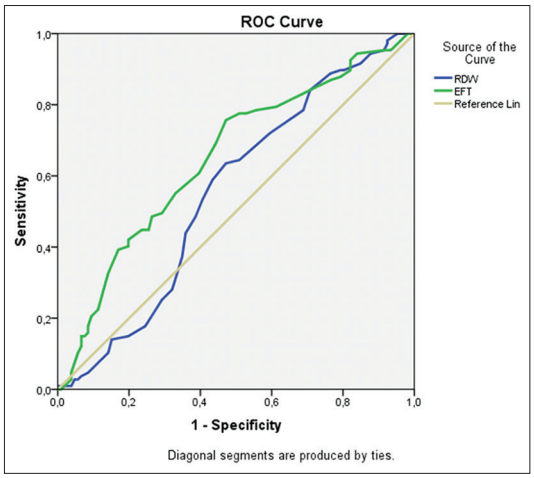


Figure 2: Receiver-operating characteristic curve analysis of HgA1c value to predict epicardial fat tissue ≥4.15 mm

disease.[23-25] Chronic inflammation underlying these diseases cause erythrocyte deformability and ineffective erythropoiesis which in turn leads to anisocytosis (high RDW).[4]

Diabetic patients have higher RDW values when compared with normal participants.[26] Chronic hyperglycemia occurring in DM has several effects on erythrocytes, including glycosylation of hemoglobin,[27] impaired deformability, increased aggregation, and decreased circulatory half-life.[6] Nada.[26] reported that RDW levels were significantly high in diabetic patients than in control subjects and it was positively correlated with HbA1c levels.

EFT volume is higher in males, elderly, obese persons, as well as in diabetic and metabolic syndrome patients.[28-30] Although our study and control group were similar with respect to their age, sex, and BMI values, diabetic patients had an increased EFT thickness, which showed a correlation with RDW. The cytokines secreted by EFT affect erythropoiesis, erythrocyte volume, erythrocyte lifespan, and thus promoting anisocytosis (high RDW).[31-33] It is known that glycosylation of the hemoglobin reduces the lifespan of the erythrocytes.[7,8] It can be speculated that, hormonal activity of EFT, glycosylation of hemoglobin, and increased oxidative stress in diabetic patients could cause RDW level elevation.

DM is a metabolic disease which imposes substantial socioeconomic burden as a result of its complications. We showed that type II diabetic patients had higher EFT thickness and RDW levels when we compared them with the normal individuals. Moreover, EFT thickness was positively correlated with RDW. It has been shown that both EFT and RDW have prognostic value for ischemic heart disease, in-stent restenosis, congestive heart failure, and peripheral arterial disease. Therefore, measurement of EFT thickness and RDW in patients with DM may provide additional prognostic information.

Limitations

The limitations of the study include the following: (1) It was a single-center study; (2) the study contained a relatively small number of patients; (3) EFT thickness was not measured by multislice CT and/or magnetic resonance imaging in our study patients; (4) we did not separate the diabetic patients according to their medical treatment. Hence, we could not compare the patients in two groups with insulin therapy or only oral antidiabetics; and (5) we did not evaluate the duration of disease, we could not make the correlation analysis between disease duration and EFT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Initial T Wave Morphology in the Chest Leads in Patients Presenting with Anterior ST-Segment Elevation Myocardial Infarction and its Correlation with Spontaneous Reperfusion of the Left Anterior Descending Coronary Artery

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Abstract

Background: T wave inversion in leads with ST-segment elevation after reperfusion therapy is considered a sign of reperfusion. However, the significance of T wave inversion on presentation before the initiation of reperfusion therapy is unclear. **Aim of the Work:** The current study aimed to assess whether the initial T wave morphology in the electrocardiographic (ECG) at presentation can predict patency of the left anterior descending artery (LAD) in patients with acute anterior ST segment elevation myocardial infarction (STEMI) before undergoing primary percutaneous coronary interventions (PCIs). **Methods:** This study included ninety patients who presented to the emergency department with acute anterior ST-elevation MI. We excluded patients with bundle branch block, postcoronary artery bypass grafting patients, patients with paced rhythm, and patients who received thrombolytic therapy. The T wave morphology in the 2 leads with maximal ST-segment elevation on the presenting ECG was identified as one of the three morphologies, positive T waves (T+; initial positive deflection ≥0.5 mm above the isoelectric line), biphasic T waves (T+/−; where the T wave initially showed a positive deflection above the ST segment afterward followed by a negative deflection ≥0.5 mm below the isoelectric line), and negative T waves (T−; where the T wave initially showed a negative deflection ≥0.5 mm below the isoelectric line without showing any initial positive deflection). Then, according to the results of the initial angiography, patients were classified into spontaneous reperfusion (SR) (those with thrombolysis in MI [TIMI] II or TIMI III flow in the infarct-related artery [IRA] prior to intervention) or non-SR (those with TIMI 0 or TIMI I flow in the IRA prior to intervention). **Results:** Ninety consecutive patients (77 males and 13 females) presented by STEMI and treated by primary PCI at cath lab of Ainshams University Hospitals (a 24/7 tertiary referral center for primary PCI) between January 2015 and March 2016 were included in this study, of which 40 patients (44.4%) had positive T waves (T+), 34 patients (37.8%) had negative T waves (T−), and 16 patients (17.8%) had biphasic T waves (T+/−). Initial angiogram showed that 18 patients had SR and 72 patients had no SR. With regard to T wave morphology, negative T waves were significantly present in SR group (66.7% vs. 30.6%, $P = 0.004$), whereas positive T waves were predominantly present in non-SR (50% vs. 22.2%, $P = 0.033$). **Conclusions:** For SR of LAD in anterior STEMI patients, prior to primary PCI, T wave inversion had a good sensitivity of 66.7%, a specificity of 69.4%, and a good negative predictive value of 89.29%.

Keywords: Anterior ST-segment elevation myocardial infarction, spontaneous reperfusion, T wave

Introduction

Myocardial infarction (MI) can be diagnosed clinically by chest pain and other characteristics, electrocardiographic (ECG) changes, elevated levels of biomarkers of myocardial necrosis, and by imaging, or

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finally by pathological identification of myocardial tissue necrosis.[1]

The ECG is the primary diagnostic tool used to identify ST-segment elevation MI (STEMI) that is necessary and crucial because it identifies those patients who are candidates for emergent reperfusion therapy. The fourth universal definition of MI, defined by the Joint Committee of American College of Cardiology (ACC) and the European Society of Cardiology (ESC) for the redefinition of MI, is a new, or presumed new, ST segment elevation in 2 or more contiguous leads of at least 2 mm at the J point in leads V1–V3 or 1 mm in other leads.[1]

Anterior STEMI results from occlusion of the left anterior descending artery (LAD). Anterior MI carries the worst prognosis of all infarct locations, mostly due to larger infarct size. The nomenclature of anterior infarction can be confusing, with multiple different terms used for the various infarction patterns. The different infarct patterns are named according to the leads with maximal ST elevation, septal infarction with the maximal ST elevation in the chest leads V1–2, anterior with the maximal ST elevation in the chest leads V2–5, anteroseptal with the maximal ST elevation in the chest leads V1–4, anterolateral with the maximal ST elevation in the chest leads V3–6, I + aVL, and finally extensive anterior/anterolateral with the maximal ST elevation in the chest leads V1–6, I + aVL. Although these definitions are intuitive, there is often a poor correlation between ECG features and precise infarct location as determined by imaging or autopsy.[2]

The current guidelines for the treatment of ST-segment elevation MIs (STEMI) emphasize the importance of shortening the time interval between the occlusion of the infarct-related artery (IRA) and reperfusion to salvage myocardium and minimize infarct size.[3]

In patients with ST-elevation MI (STEMI) undergoing primary percutaneous coronary intervention (PCI), a patent IRA on initial angiography was associated with better angiographic results and improved prognosis compared with patients without spontaneous restoration of the blood flow. Little is known about the prevalence, clinical course, and optimal management of patients presenting with clinical signs of spontaneous reperfusion (SR). SR is defined as a ≥70% reduction in ST elevation and pain severity before the initiation of reperfusion therapy.[2] Although patients with SR of the IRA have a higher incidence of recurrent in-hospital ischemia, on the longer term, they develop smaller MIs and sustained less in-hospital cardiogenic shock, less incidence of heart failure, and less electrical and arrhythmic complications and have a lower 7- and 30-day mortality rates.[4] SR remains significantly associated with a lower incidence of the combined end point of 30-day death, heart failure, and recurrent MI. The outcome of patients who were found to have SR is markedly better than those patients without SR who underwent primary PCI, despite the initial conservative management.[5]

SR in ST-elevation MI has traditionally been assessed by coronary angiography. The frequency of SR varies widely in prior studies, and the clinical implications in the modern reperfusion era are unclear.[2,4,5]

Negative T waves (T−) in the leads with maximum ST-segment elevation early after initiation of reperfusion therapy whether by thrombolysis or by primary PCI have been described as a marker of reperfusion and a good prognostic sign.[4]

However, the significance of T wave inversion on presentation before the initiation of reperfusion therapy and patency of the IRA (thrombolysis in MI [TIMI] flow grades) is unclear.[6]

Methods

We performed a prospective, single-center observational study at Ainshams University Hospitals, a tertiary referral hospital with a 24/7 primary PCI service offered to all incoming STEMI patients. Ninety consecutive patients admitted from February 2014 to December 2015 from the ED with the diagnosis of anterior STEMI in accordance with the ESC guidelines were included.[1] The study protocol was approved by the local Institutional Ethical Committee. This study included ninety patients who presented to the emergency department with acute anterior ST-elevation MI. We excluded patients with bundle branch block, postcoronary artery bypass grafting patients, patients with paced rhythm, and patients who received thrombolytic therapy. The T wave morphology in the 2 leads with maximal ST-segment elevation on the presenting ECG was identified as one of the three morphologies as shown in Figures 1-3, respectively, positive T waves (T+; initial positive deflection ≥0.5 mm above the isoelectric line), negative T waves (T−; where the T wave initially showed a negative deflection ≥0.5 mm below the isoelectric line without showing any initial positive deflection), and biphasic T waves (T+/−; where the T wave initially showed a positive deflection above the ST segment afterward followed by a negative deflection ≥0.5 mm below the isoelectric line). Then, according to the results of the initial diagnostic angiography prior to intervention, patients were classified into SR (those with TIMI II or TIMI III flow in the IRA prior to intervention) or non-SR (those with TIMI 0 or TIMI I flow in the IRA prior to intervention).

All data were summarized and displayed as mean ± standard deviation for continuous variables and as number (percentage) of patients in each group for categorical variables. The *P* values for the categorical variables were calculated with the Chi-square test. Continuous variables were compared using the independent sample *t*-test. A two-tailed $P < 0.05$ was considered statistically significant for all analyses. All analyses were performed with the SPSS software (SPSS Inc., Chicago, Illinois, USA).

Results

According to the occurrence of SR found upon the initial coronary angiogram prior to performing any intervention in

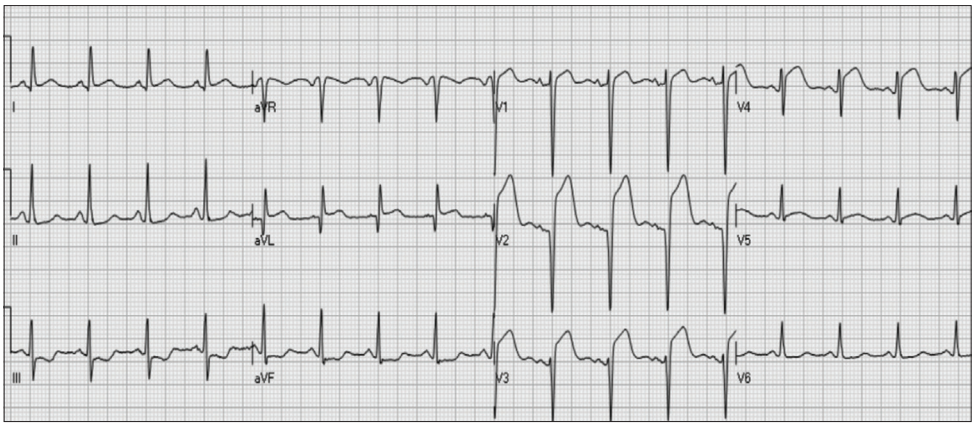


Figure 1: Positive T waves: T+; initial positive deflection ≥0.5 mm above the isoelectric line

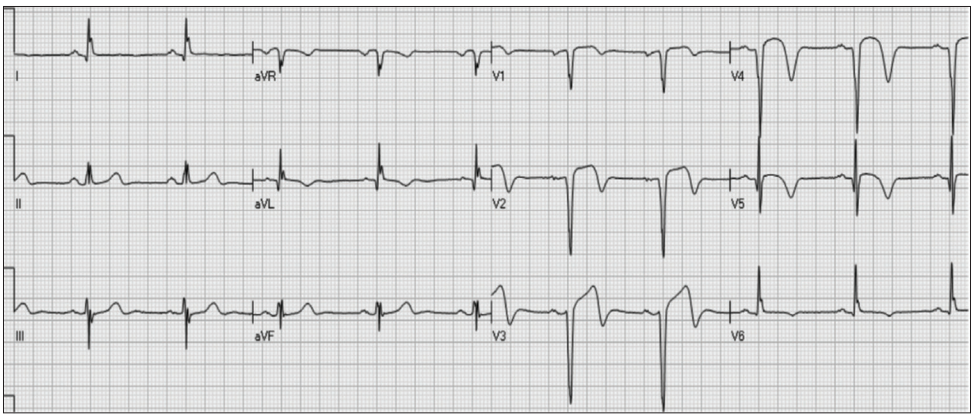


Figure 2: Biphasic T waves: T+/−; initial positive deflection above the ST segment followed by negative deflection ≥0.5 mm below the isoelectric line

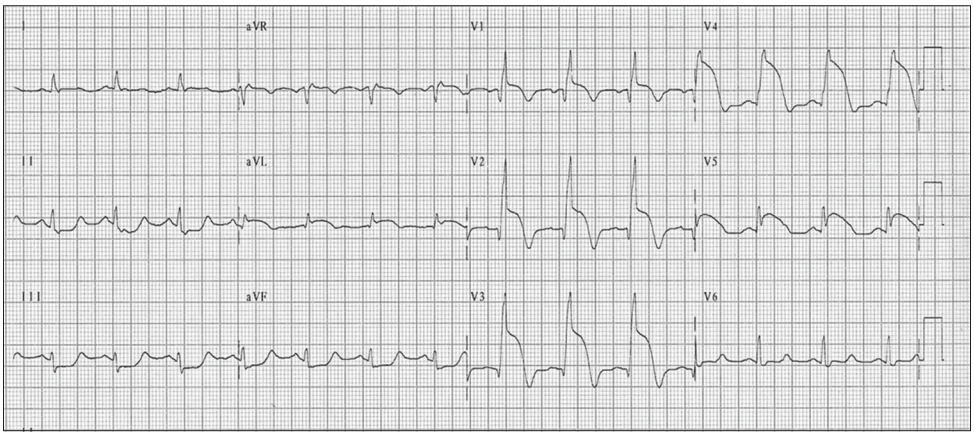


Figure 3: Negative T waves: T−; initial negative deflection ≥0.5 mm below the isoelectric line without initial positive deflection

the primary PCI procedure, patients were classified into two groups: SR group, those showing TIMI II or TIMI III flow in the LAD, and non-SR group, those showing TIMI I or TIMI 0 flow in the LAD.

The baseline demographic data are shown in Table 1; patients in the SR group were significantly older than those of the non-SR group (56.85 ± 10.23 years vs. 51.56 ± 9.30) ($P = 0.049$). There was no significant difference between the two groups regarding gender or any of the cardiovascular risk factors.

With regard to T wave morphology in the presenting ECG prior to revascularization by primary PCI, negative T waves were significantly present in SR group (66.7% vs. 30.6%), whereas positive T waves were predominantly present in non-SR group (50% vs. 22.2%) as shown in Table 2. There was a nonsignificant difference between the two groups regarding the biphasic T waves (T+/T−) (11.1% vs. 19.4%).

Considering the predictive value of a negative T wave (T−) versus a nonnegative T wave (T + or T+/−), the finding of a

Table 1: Comparison between the demographic data of the two groups

	Spontaneous reperfusion (*n*=18), *n* (%)	Nonspontaneous reperfusion (*n*=72), *n* (%)	Independent *t*-test	
			t/χ^2*	*P*
Age, mean±SD	56.85±10.23	51.56±9.30	1.997	0.049
Sex				
Females	9 (12.5)	4 (22.2)	1.101*	0.294
Males	63 (87.5)	14 (77.8)		
DM				
Yes	30 (41.7)	9 (50.0)	0.407*	0.523
No	42 (58.3)	9 (50.0)		
HTN				
Yes	38 (52.8)	11 (61.1)	0.403*	0.525
No	34 (47.2)	7 (38.9)		
Smoking				
Yes	53 (73.6)	10 (55.6)	2.235*	0.135
No	19 (26.4)	8 (44.4)		
Dyslipidemia				
Yes	53 (73.6)	11 (61.1)	1.095*	0.295
No	19 (26.4)	7 (38.9)		
FH				
Yes	35 (48.6)	8 (44.4)	0.100*	0.752
No	37 (51.4)	10 (55.6)		

*Significant. SD: Standard deviation, HTN: Hypertension, DM: Diabetes mellitus, FH: Familial hypercholesterolemia

Table 2: Comparison between the two groups regarding T wave morphology

T wave morphology in leads with maximum ST elevation	Spontaneous reperfusion, *n* (%)	Nonspontaneous reperfusion, *n* (%)	Chi-square test	
			χ^2	*P*
Negative	12 (66.7)	22 (30.6)	8.033	0.018
Biphasic	2 (11.1)	14 (19.4)		
Positive	4 (22.2)	36 (50.0)		

predominantly negative T wave (T−) on the initial presenting ECG prior to revascularization by primary PCI had a good sensitivity (66.7%) and specificity (69.4%) with good negative predictive value (89.29%) and a weak positive predictive value (35.29%), as shown in Table 3.

Table 3: The predictive value of a predominantly negative T wave on the initial presenting electrocardiography

	Spontaneous reperfusion, *n* (%)	Nonspontaneous reperfusion, *n* (%)	Chi-square test	
			χ^2	*P*
Negative	12 (66.7)	22 (30.6)	7.988	0.004
Nonnegative	6 (33.3)	50 (69.4)		

Discussion

This prospective, single-center observational study at Ainshams University Hospitals included a cohort of ninety patients presented by STEMI who underwent primary PCI for revascularization as per guidelines (3). We intended to identify whether the initial T wave morphology in the ECG at presentation can predict patency of the LAD in patients with acute anterior ST-segment elevation MI (STEMI) before undergoing revascularization by primary PCI.

We found that, regarding the initial T wave morphology in the presenting ECG prior to revascularization by primary PCI, negative T waves were significantly present in SR group, whereas positive T waves were predominantly present in non-SR group. Moreover, the presence of a predominantly negative T wave (T−) on the initial presenting ECG prior to revascularization by primary PCI had a good sensitivity (66.7%) and specificity (69.4%) with good negative predictive value (89.29%) for SR.

The diagnostic value of the first ECG to estimate the true disease onset of STEMI has been suggested previously.[2] T wave inversion and pathological Q waves develop later in the STEMI course, suggesting that more hours have passed the start of the pathological process of STEMI. It is difficult to know accurately the precise time of acute vessel occlusion if the patient cannot differentiate preinfarct angina from the chest pain due to acute STEMI caused by the acute coronary arterial occlusion.[2]

According to the most recent ESC and ACC guidelines for the treatment of STEMI and also in concordance with the previous versions of the myocardial revascularization guidelines, it is the first priority to shorten the time interval between the occlusion of the IRA and opening the IRA to restore the blood flow and reperfuse the myocardium affected to salvage myocardium and minimize infarct size.[3] This halts the rapid progression of myocardial necrosis because of the presence of ongoing transmural ischemia. Yet, still in some patients presenting with ST-segment elevation, SR, even partially, not necessarily TIMI III, even TIMI II, may abort the progression of myocardial necrosis.[4] The value of stenting in those cases is actually to prevent acute vessel re-occlusion, hence reducing the incidence of reinfarction, rather than immediate myocardial salvage. Hence, in such patients presented by STEMI, if they were stable upon presentation, we may lengthen the door to balloon time beyond the current recommendation of 90 min, similar to the approach for non-STEMI (NSTEMI) cases, where in fact a subset described as those with transient ST segment elevation – but not persistent ST segment elevation – are high-risk NSTEMI mandating intervention within 120 min.[7] Reduction in the severity of symptoms, mainly relief of chest pain, may indicate reperfusion, the presenting symptoms maybe atypical in the elderly, females, patients receiving analgesics, and diabetic patients. ECG changes in such cases probably is a better indicator of reperfusion including ST segment resolution, more than 70% from the initial ECG at presentation. According to the guidelines, a persistent ST segment elevation (even if there is >70% resolution in the magnitude of ST-segment elevation compared with the first ECG), emergency primary PCI is indicated, and the issue of SR is not addressed.

Early after reperfusion therapy, the morphology of the T waves in the 12-lead surface ECG focusing on the leads with maximum ST-segment elevation has been described as a positive finding indicating coronary artery reperfusion, and this has a good prognostic implication.[6,8] However, it is worth mentioning that T wave inversion is actually a part of the natural evolution of the ECG changes in STEMI regardless of they received reperfusion therapy or not.[9,10] In these cases, T wave inversion, in association with pathological Q waves, represents a marker of an already evolved MI.[9]

Herz *et al*.[11] found that, in patients who received tenecteplase for thrombolysis, a predominantly negative T wave in the 12-lead surface ECG, examined and analyzed in the leads that showed highest ST segment elevation, was associated with better outcomes in the form of reduced mortality in those receiving fibrinolytic therapy in the early golden hours' time window, within the first 2 h of the start of symptoms, mainly measured from the onset of chest pain. On the other hand, regarding the patients who were treated later, within 2–6 h after the onset of chest pain, T wave inversion was associated with worse outcomes in the form of increased mortality, a finding that can be attributed to the reduced efficacy of thrombolytic therapy after the first 2 h.[11]

Conclusions and Study Limitations

For SR of LAD in anterior STEMI patients, prior to primary PCI, negative T waves were significantly present in SR group (66.7% vs. 30.6% with $P = 0.004$), whereas positive T waves were predominantly present in non-SR group (50% vs. 22.2% with $P = 0.033$). T wave inversion had a good sensitivity of 66.7%, a specificity of 69.4%, and a good negative predictive value of 89.29%.

There are several important limitations of this study. This was a single-center, prospective, and nonrandomized observational study on a small cohort of patients. A long-term follow-up would have added data upon the long-term outcomes of revascularization of primary PCI-treated patients comparing the SR versus the non-SR group.

Further and larger studies are needed to confirm whether the combination of symptom relief; ST-segment resolution >50% from the initial magnitude of ST segment elevation; and the T wave morphology whether positive, negative, or biphasic are accurate enough to determine whether there is a difference in the long-term outcomes of primary PCI between these two subsets of patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Original Article

Differences in Atrial Fibrillation Management Strategies among Physicians: A Survey Based Study

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Abstract

Aim: Previous data reflected confusions about classification and management of atrial fibrillation (AF) among physicians. Although relatively clear suggestions of dedicated guidelines, poor adaptation of them to routine clinical practice may result with suboptimal prevention and treatment measures. As a main stakeholder of management, physicians' perceptions about the disease have major role. The study aimed to assess confusions and concordances of physicians about the definition and management of the disease. **Methods and Results:** We developed a web-based survey about AF consisting of 27 questions regarding valvular or non-valvular AF perception, using thromboembolic and bleeding risk scores, antithrombotic management and rate/rhythm control strategies. Two hundred and thirty two physicians participated and 224(97%) of them completed the survey. Although only cardiologists were invited to the survey, 27 physicians from different specialties also responded the survey. Half of the physicians reported that ≥40% of their patients had valvular AF. Dramatically, the survey responses revealed that nearly one-third of physicians classified the AF patients with mitral regurgitation as valvular AF. Most of the physicians denoted that they were using bleeding and stroke risk scores before deciding oral anticoagulation therapy and also preferring long term rhythm-control strategy in AF patients with systolic heart failure. However, results exposed evident disparities among physicians at specific aspects of the disease management. **Conclusion:** The survey-based study demonstrated a great heterogeneity in classification and management of AF among physicians because of guideline confusions/failures, inadequate evidence about some specific conditions and not being able to dominate the guidelines by physicians.

Keywords: Atrial fibrillation, management, physician, survey

Introduction

Atrial fibrillation (AF) is an independent risk factor for stroke and a significant predictor of mortality. Evidence-based AF guidelines recommend antithrombotic therapy corresponding to the risk of stroke.[1] In practice, many patients with AF do not receive the appropriate antithrombotic therapy and are left either unprotected or inadequately protected against the risk of stroke.[2] Valvular AF has gained importance after the introduction of non-Vitamin K antagonists (NOACs) taking into account their contraindications.[3] The current guidelines have provided clear definition of the valvular AF.[1] Previous physician surveys showed heterogeneity in the perception of valvular AF

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and variable thromboprophylactic strategies among physicians, particularly in the case of mitral regurgitation.[4] Furthermore, recent European Heart Rhythm Association (EHRA) survey showed striking discordances in the definition and assessment strategies of valvular AF.[3] The treatment threshold for the use of oral anticoagulants (OAC) differs between the current guidelines. Similarly, there is a controversy among the current guidelines regarding antithrombotic agent selection. Although according to the ACC/AHA/HRS guidelines aspirin (ASA) continues to have a role in the treatment of patients who have low stroke risk and cannot use OACs, the European Society of Cardiology (ESC) guidelines have entirely eliminated the use of ASA.[1,5] These controversies in the guidelines may lead to significant differences in patient management in clinical practice.

NOACs have been emerged as an alternative to Vitamin K antagonists (VKAs) for thromboembolic prevention in AF patients. However, compared with VKAs, the proper use of NOACs requires many practical aspects. Practical guidelines about how to deal with NOACs in specific clinical situations have been published and updated by The European Heart Rhythm Association in recent years.[6,7] Implementation of this guidance in clinical practice remained unclear.

The purpose of the survey was to obtain possible discrepancies on perception and management strategies of AF expressed by physicians in Turkey.

The methodology of the survey

We prospectively conducted a web-based survey for the opinions of physicians about AF. The study population was selected from a database composed of physicians who attended to the scientific activities of Society of Cardiovascular Academy. An electronic link of the questionnaire was sent to their E-mail addresses. The link deactivated after 6 months. The survey was voluntary, and no grant was given to the participants. Informed consent to participate in the survey and publication of the data was obtained by all involved physicians through Q26.

Questionnaire development

The questionnaire was developed by the second and last authors. Most of the questions were based on a multiple choice format. Due to the structure of the electronic questionnaire, skipping to the next question without giving an answer to the current question had not been allowed. The study was conducted according to the Declaration of Helsinki and its subsequent modifications. The demographic and personal data of each physician participated in the present survey were carefully preserved and strictly protected. The study was approved by the local ethics committee (Ege University, 26/01/2017-E.21845, 17-1.1/2).

Survey questionnaire

The survey questionnaire included a total of 26 questions addressing the following items: (1) Occupational demographics of physicians (Q01–Q05); (2) Perception of valvular AF (Q06–Q09); (3) Using stroke, bleeding risk scores and antithrombotic management strategies (Q10–Q12, Q16–Q17-Q20); (4) OAC therapy at specific scenarios (Q14–Q15, Q18, Q21–Q25); (5) Rhythm/Rate Control Strategies (Q13, Q19). The questionnaires were completed between January 2017 and July 2017.

Table 1: Occupational demographics of physicians participating in the survey

Question (n/text)	Answers, *n* (%)
Q1. What is your area of expertise?	
Cardiology	197 (87.95)
Cardiovascular surgery	10 (4.46)
Internal diseases	5 (2.23)
Neurology	3 (1.34)
Emergency	3 (1.34)
Family medicine	6 (2.68)
Q2. How many years do you work as a physician?	
<5	20 (8.93)
5-10	79 (35.27)
>10	125 (55.80)
Q3. What is your academic status?	
Trainer	17 (7.59)
Specialist	127 (56.70)
Assistant professor	23 (10.27)
Associated professor	37 (16.52)
Professor	20 (8.93)
Q4. In which institution are you working?	
Private hospital/medicine center	43 (19.19)
Education Research Hospital, State Hospital	15 (51.34)
University	61 (27.23)
Family health center	5 (2.23)
Q5. How often do you experience atrial fibrillation in 1 month?	
5%-10%	67 (29.91)
11%-20%	87 (38.84)
21%-30%	53 (23.66)
31%-40%	10 (4.46)
>40%	7 (3.13)

Data analysis

Data were collected within the SurveyMonkey web site, exported to Excel (Microsoft, Redmond, WA) format, and imported into IBM SPSS (version 22.0 for Windows, Armonk, NY, USA) for statistical analysis. The answers to all questions were summarized as frequency counts and percentages. Because of the structure of the questionnaire, unanswered questions were not possible.

Results

The physician population included 197 cardiologists (88%), 10 cardiovascular surgeons (4.5%), 6 family physicians (2.7%), 5 internists (2.2%), 3 neurologists (1.3%), and 3 emergency physicians (1.3%). Of the 224 respondents, 125 (55.8%) had been in practice for >10 years, and 115 (51.3%) of them were working in education, research, and state hospital. Distribution of their academic degrees was as follows: 127 (56.7%)

specialists, 37 (16.5%) associated professors, 23 (10.3%) assistant professors, 20 (8.9%) professors, and 17 (7.6%) trainees. Occupational demographics of the population are detailed in Table 1.

Half of the physicians estimated that nonvalvular AF would account for ≥40% of all AF patients. A minority of the physicians (8.5%) thought that AF was valvular when associated with mitral regurgitation irrespective of its etiology and severity. Interestingly, 28% of physicians submitted that they decided valvular or nonvalvular AF according to the severity of mitral regurgitation [Figure 1]. While 74% of the physicians did not consider ischemic mitral insufficiency as valvular AF, 14% of them accepted 3rd degree and more mitral insufficiency as valvular AF. Nearly 43% of the physicians thought that mitral insufficiency did not decrease the risk of thrombosis in the left atrium and appendix [Table 2].

Although 63% of physicians preferred to use OACs in AF patients who had CHA_2DS_2VASc score 1 for males (two for females), 21% of them specified ASA preference. Majority of physicians remarked CHA_2DS_2VASc score (97%) using for stroke risk classification and HAS-BLED score using (83%) for bleeding risk. The proportion of physicians using other bleeding risk scores was only 3%. While 26% of the physicians preferred ASA in older patients, more than half of the physicians did not prefer ASA in AF. Most of the physicians (71%) preferred to use CHA_2DS_2VASc ≥2 for the initiation of OACs in females with AF. According to almost half of the physicians, the daily doses of the NOACs (once or twice a day) were not important, but the other half of them did not agree [Table 3].

More than half of the physicians did not change doses of warfarin at the level of 1.9 INR in elderly patients. About 38% of physicians did not accept contraindications about OACs. About 48% of physicians did not prefer to use OACs therapies if the patient had any history of intracranial hemorrhage. In addition, 30% of the physicians did not consider giving OACs treatment in patients with a history of gastrointestinal bleeding. Nearly two-thirds of the physicians preferred to switch NOAC to warfarin if renal functions had decreased due to chronic diseases. In the case of the acute coronary syndrome, 75% of physicians pointed out clopidogrel preference in AF patients using OACs.

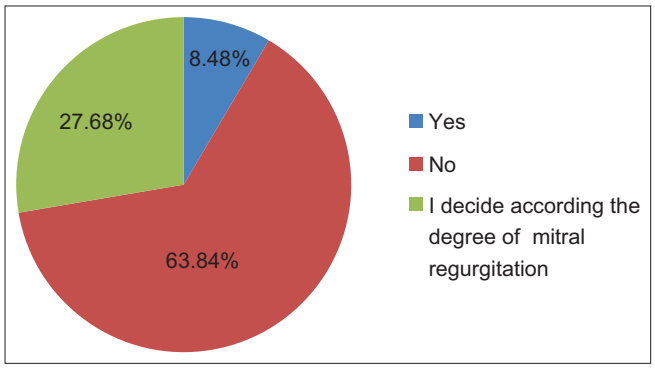


Figure 1: The ratio of physicians answering mitral regurgitation with atrial fibrillation patients as Valvular-atrial fibrillation

Only two physicians responded prasugrel preference [Figure 2]. More than half of the physicians considered switching warfarin to NOACs in AF patients who had low TTR levels, stroke/transient ischemic attack (TIA)/bleeding under warfarin and

Table 2: Perception of nonvalvular atrial fibrillation by physicians

Question (*n*/text)	Answers, *n* (%)
Q6. How many percentage of the cases you accept as NVAF?	
5-10	29 (12.95)
11-20	20 (8.93)
21-30	33 (14.73)
31-40	30 (13.39)
>40	112 (50.00)
Q7. Can patients with unknown mitral valve diseases that have only mitral regurgitation (rheumatic and nonrheumatic) be classified as valvular atrial fibrillation?	
Yes	19 (8.48)
No	143 (63.84)
Decision according to the degree of mitral insufficiency	62 (27.68)
Q8. What is the degree of mitral insufficiency for the diagnosis of valvular atrial fibrillation in patients with ischemic mitral insufficiency?	
≥1°	2 (0.89)
≥2°	16 (7.14)
≥3°	33 (14.73)
Ischemic MR is NVAF	166 (74.11)
No idea	7 (3.13)
Q9. Does mitral insufficiency decrease the thrombus formation in LA/LAA in patients with AF?	
Yes	41 (18.30)
No	97 (43.30)
Only LA	41 (18.30)
Both of them	30 (13.39)
No idea	15 (6.70)

NVAF: Nonvalvular AF, LA: Left atrium, LAA: Left atrial appendage

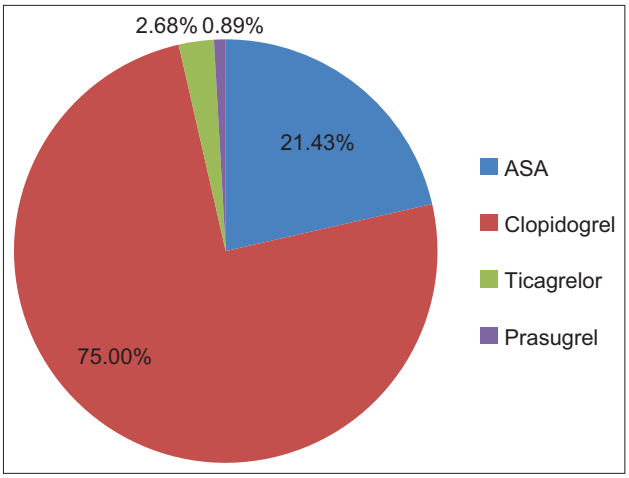


Figure 2: Antiplatelet agent preferences of physicians in atrial fibrillation patients using oral anticoagulants during acute coronary syndromes

Table 3: Using of stroke and bleeding risk scores and antithrombotic management strategies

Question (*n*/text)	Answers, *n* (%)
Q10. What do you begin CHA_2DS_2VASc score of 1 for males and CHA_2DS_2VASc score of 2 for females in NVAF?	
Only ASA	46 (20.54)
OAC (VKA or NOAC)	141 (62.95)
No medical treatment	37 (16.52)
I have no idea	-
Q11. When you decide anticoagulant therapy in your daily practice NVAF, what scoring system do you use (for stroke risk)?	
CHADS2	3 (1.34)
CHA2DS2VASc	218 (97.32)
None	3 (1.34)
Q12. Which risk scoring system do you use to determine the risk of bleeding in the NVAF patients in your daily practice?	
HAS-BLED	187 (83.48)
ATRIA	1 (0.45)
ORBIT	1 (0.45)
ABC	-
HEMORR2HAGES	5 (2.23)
None	30 (13.39)
Q16. Do you prefer antiplatelet therapy in your AF patients for protection from stroke?	
Continue if drugs started before	41 (18.30)
No	125 (55.80)
Sometimes only old patients	58 (25.89)
Q17. What is the limit of your CHA_2DS_2VASc score to start oral anticoagulant therapy in a female patient with AF?	
≥1	19 (8.48)
≥2	159 (0.98)
≥3	46 (20.54)
Q20. Does single or double dose use affect your choice of NOAC?	
Yes	110 (49.11)
No	108 (48.21)
I have never used	6 (2.68)

AF: Atrial fibrillation, NVAF: Nonvalvular AF, NOAC: NonVitamin K antagonist oral anticoagulant

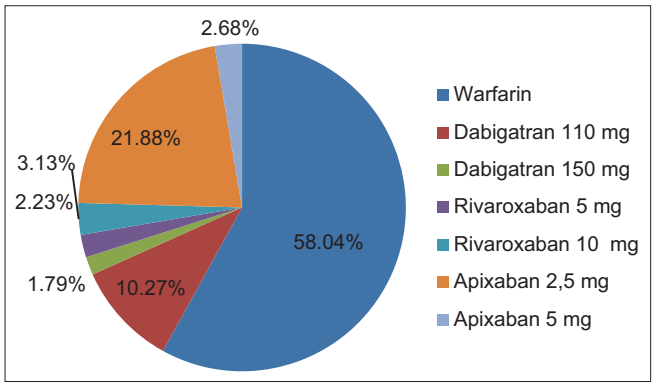


Figure 3: Physicians oral anticoagulants' preferences in atrial fibrillation patients with creatinin clearance <30 ml/dk

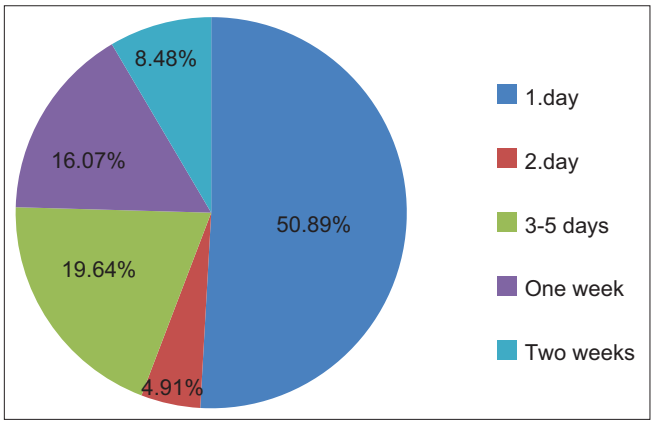


Figure 4: Oral anticoagulants therapies Initiation times by physicians after transient ischemic attack in patients with atrial fibrillation

incompatibility. Furthermore, most of the physicians have thought to switch NOACs to warfarin in these conditions; drug side effects, stroke, and bleeding under NOACs. About 58% of the physicians preferred warfarin in AF patients with severe kidney diseases who had CHA_2DS_2VASc score of 3 and HASBLEED score of 2. The second preferred drug was apixaban 2.5 mg in severe kidney diseases by physicians (22%) [Figure 3]. Half of the physicians considered to start anticoagulation after the 1st day in AF patients with transient ischemic stroke [Figure 4 and Table 4].

Most of the physicians selected propafenone and amiodarone as the first-line agents for cardioversion (CV) in paroxysmal AF. Beta-blockers and digoxin were chosen by the majority of physicians (91% and 71%, respectively) as rate control

Table 4: Oral anticoagulant therapy at different scenarios

Question (*n*/text)	Answers, *n* (%)
Q14. What do you do if you detected 1, 9 INR levels in eighty or above ages patient under warfarin treatment?	
I decrease	3 (1.34)
I increase	99 (44.20)
I do not change	122 (54.46)
Q15. Which of the following factors is reason for not giving OAC despite the indication of oral anticoagulant treatment?	
Advanced age	21 (9.38)
Risk of patient failing	26 (11.61)
Education level	41 (18.30)
Renal failure (stage 3 and above)	41 (18.30)
History intracranial hemorrhage	107 (47.77)
Major GIS bleeding history	67 (29.91)
None	86 (38.39)
Q18. What do you do if renal functions of NVAF patient under NOAC therapy show progressive deterioration due to underlying chronic diseases (HT, DM, Vascular disease, etc.,) (GFR<30 ml/min)?	
Continue low dose of NOAC	68 (30.36)
Change to warfarin	145 (64.73)
Not medicate (OAC)	11 (4.91)
Q20. Use single or double dose per day, do you influence your choice of NOAC?	
Yes	110 (49.11)
No	108 (48.21)
I have never used	6 (2.68)
Q21. Which antiplatelet agent do you prefer with oral anticoagulant therapy after acute coronary syndromes in AF patients?	
ASA	48 (21.43)
Klopidogrel	168 (75)
Tikagrelor	6 (2.68)
Prasugrel	2 (0.89)
Q22. Which cases do you switch warfarin to NOAC in NVAF patients? (Multiple options can be marked)	
Directly	40 (17.68)
Low TTR levels (<65%)	191 (85.27)
Stroke/TIA under warfarin therapy (although optimum INR levels)	148 (66.07)
Hemorrhage under warfarin therapy	138 (61.61)
Patients does not want to follow INR levels	166 (74.11)
Limitation of logistics requirements	184 (82.14)
Never	2 (0.89)
Q23. Which situations do you switch NOAC therapy to other NOAC therapy or warfarin in NVAF patients? (multiple options can be marked)	
Stroke/TIA associated therapy	180 (80.36)
Hemorrhage associated therapy	172 (76.79)
Side effect associated therapy	203 (90.63)
No changing (focusing in trigger factors)	16 (7.14)
Q24. Which OAC do you prefer in AF patients that have 3 CHA2DS2-VASc score and 2 HAS-BLEED score if their creatinine clearance lowers 30 ml/min?	
Warfarin	130 (58.04)
Dabigatran 110 mg	23 (10.27)
Dabigatran 150 mg	4 (1.79)
Rivaroxaban 5 mg	5 (2.23)
Rivaroxaban 10 mg	7 (3.13)
Apixaban 2, 5 mg	49 (21.88)
Apixaban 5 mg	6 (2.68)
Q25. How many days after do you recommend oral anticoagulant therapy to AF patients with transient ischemic stroke?	
1 day	114 (50.89)
2 days	11 (4.91)
3-5 days	44 (19.64)
1 week	36 (16.07)
2 weeks	19 (8.48)

INR: International normalized ratio, AF: Atrial fibrillation, NVAF: Nonvalvular AF, NOAC: Nonvitamin K antagonist oral anticoagulant, OAC: Oral anticoagulant, GIS: Gastro-intestinal system, GFR: Glomerular filtration rate, TIA: Transient ischemic attack

Table 5: Rhythm/rate control strategies

Question (*n*/text)	Answers, *n* (%)
Q13.What is your first drug option in the pharmacological cardioversion of paroxysmal atrial fibrillation?	
Beta blockers	31 (13.84)
Propafenone	91 (40.63)
Amiodarone	92 (41.07)
Verapamil-diltiazem	7 (3.13)
Digoxin	3 (1.34)
Q19. Which option do you prefer in AF patients that have ejection fraction below 40% for long-term heart rate control? (multiple options can be marked)	
Digoxin	159 (70.98)
Amiodarone	39 (17.41)
Beta blockers	203 (90.63)

agents in AF patients with low ejection fraction [Table 5]. The last two questions (Q26, Q27) were about consent and address information.

Discussion

This survey has provided information about confusions and compatibilities of valvular and nonvalvular AF and usage of bleeding and risk scores in real life during the management of AF patients. In addition, the survey obtained physicians' perspectives in terms of managing specific AF patient groups and in special situations.

The definition of valvular and nonvalvular AF has become more important after emerging of NOACs. Previous guidelines defined nonvalvular AF in the absence of a mechanical prosthetic heart valve or moderate to severe mitral stenosis[8,9] (usually of rheumatic origin). The trials about NOACs have excluded mechanical prosthetic heart valve and mitral stenosis.[10] In this study, half of the physicians accepted >40% of the patients were nonvalvular AF. These can be explained in three ways: (1) high prevalence of rheumatic valve diseases in our country due to the frequency of acute rheumatic fever, (2) nomenclature confusion of studies in literatures, and (3) physicians do not dominate the definitions in the current guidelines and are affected by the nomenclature confusions. More than half of the physicians in this survey evaluated mitral regurgitation as nonvalvular AF in patients with AF. Unlike this survey, in a previous study, most participants agreed that rheumatic mitral regurgitation was related to valvular AF.[3] Perceptions of valvular AF are different among the studies because guidelines have different attitudes in valvular abnormalities other than prosthetic valves and mitral stenosis. Different designs of recent trials about NOACs led to confusions, gray zones in guidelines. While RELY trial excluded hemodynamically relevant valve diseases, ROCKET-AF study included patients who underwent annuloplasty, valvuloplasty, and commissurotomy. Furthermore, ARISTOTLE and ENGAGE trials did not include patients with moderate-to-severe mitral stenosis.[11] Therefore, 2016 ESC guideline eliminated valvular AF to avoid confusion.[1]

Some risk scoring methods were developed to evaluate the risk of stroke in the late 1990s in small cohort studies. The most commonly used and recommended score system by ESC guidelines is CHA_2DS_2VASc score. This scoring method firstly took place in ESC guidelines in 2010.[12,13] In the light of the guidelines, almost all physicians (97%) preferred CHA_2DS_2VASc scoring method in AF patients. More than half of the physicians agreed to start OACs with CHA_2DS_2VASc score of 1 for males and 2 for females. In a previous study, most of the physicians (78%) thought that no additional research for starting anticoagulants when CHA_2DS_2VASc score ≥1 in AF patients.[14] Some studies have shown that CHA_2DS_2VASc score of ≥1 for male and CHA2DS2VASc score of ≥2 for females was related with stroke and they would benefit from oral anticoagulant agents. OACs should be considered for patients after balancing the expected stroke risk, bleeding risk, and patient preference.[6,15] In this survey, 70% of the physicians accepted the anticoagulant starting limit as CHA_2DS_2VASc of ≥2 for females, but current guidelines revealed that female gender alone does not appear to increase stroke risk in the absence of other stroke risk factors.[16,17] There are some differences about the risk scoring system among guidelines. Unlike the American guidelines,[5] European guidelines[1] do not recommend antiplatelet agents in AF patients with a CHA_2DS_2VASc score of = 0.

Most of the physicians (83%) preferred HAS-BLED bleeding risk score in AF as this score has been derived by using a real-world cohort of 3978 AF patients and it is a simple bleeding risk score system for physicians.[18] Frequent use of bleeding risk scores by physicians in AF patients with high thromboembolic risk may be due to ensure the safety of patients. In a study, it was shown that 26% of AF patients with aged 80 years and over had stopped using OACs therapies for safety reasons in the 1st year. Especially, the intracranial hemorrhage risk related to fall is overestimated.[19]

The physicians usually gave different responses about management of the patients with AF in specific scenarios. One of them was the management of elderly patients under subtherapeutic warfarin treatment. European guidelines[1] depicted that OACs should not be avoided only due to age in elderly patients because of the higher risk of stroke in these people, but comorbidities should be taken into account. Although the most important contraindication of OAC therapies was intracranial hemorrhage in this survey, more than half of the physicians considered using OACs treatment after intracranial bleeding. Previous studies shown that less than half of the physicians have prescribed OAC therapies in geriatric syndromes, cognitive disorders and fall risk in elderly AF patients. Physicians are worried about prescribing OACs because of the high fall risk in elderly people. Furthermore, physicians feel responsible for intracranial hemorrhage after fall in the elderly patients using OACs. Hence, some physicians prefer ASA treatment in older AF patients for their safety and they consider that ASA is safer than warfarin and nearly as effective as it is. However, it has

been revealed that AF patients with high thromboembolic risk would need to fall about three hundred times a year for the risk of intracranial hemorrhage.[19] The guidelines define that intracranial hemorrhage after anticoagulant interruption causes late ischemic strokes and death. Furthermore, guidelines point out that uncontrolled hypertension, aneurysm, triple antiagregan/anticoagulant therapy is not absolute contraindication, while only spontaneous intracranial hemorrhage is precisely contraindicated for anticoagulants.[20]

While approximately two-thirds of physicians preferred to switch NOAC to warfarin, one-third of them preferred to decrease NOACs' doses in severe kidney failure diseases (glomerular filtration rate <30 ml/min/m^2). There are not adequate data on the use of NOACs for stroke prevention in AF patients with severe chronic kidney disease because NOACs trials essentially excluded patients with CrCl of <30 ml/min/m^2 (except for a few patients on apixaban with CrCl of <30 ml/min/m^2). Apixaban is approved by Food and Drug Administration in patients with creatinine clearance <15 mL/min or end-stage renal disease. However, the recommendations are based on pharmacokinetic and pharmacodynamic data of apixaban in severe kidney failure. In a meta-analysis of 43850 subjects, apixaban had a significantly lower bleeding rate than warfarin and thromboembolic event risks were similar in severe kidney diseases.[21] Today the European guidelines[22] suggest that apixaban, edoxaban, and rivaroxaban can be used in specific patients with CrCl of <30 ml/min/m^2. However, the lack of adequate trials and the difference of guidelines about renal disease may cause confusions and conflictions in physicians. Most of the physicians preferred clopidogrel as an antiplatelet agent in patients with AF who had acute coronary syndromes, 2016 ESC guideline and 2017 DAPT focused data recommends clopidogrel, ASA and NOACs as a triple therapy for acute coronary syndromes.[1] The NOACs are preferred because of their simple medication, causing less bleeding than warfarin in most cases and providing protection from stroke as warfarin.[22] For these reasons, the guidelines recommend the initiation of NOACs rather than warfarin, in patients with AF.[1]

There are no more randomized comparative trails of switching to NOACs versus VKA or NOACs treatment.[23] Switching NOAC-NOAC/NOAC-warfarin was found related to stroke and bleeding in the few previous studies. In a study, warfarin was preferred to NOACs because of previous VKA use, chronic renal failure, ischemic heart disease, and dabigatran use. The patients who preferred warfarin were young (<55) and had low CHA_2DS_2VASc score. Apixaban was tolerated by most patients using NOACs in this study. Hence, the patients who used other NOACs initially switched to apixaban during the study.[24] Users of apixaban had better persistence, this difference in persistence should be further explored. In this survey, physicians decided to switch drugs (NOAC-NOAC/NOAC-warfarin) because of stroke and bleeding under therapy (especially for secondary prevention), side effects and ease of use.

ESC guidelines[25] recommend that OACs may be continued (according to prescription and label) or started 1 day after a TIA after exclusion of intracranial bleeding by imaging modalities. However, half of the physicians in this survey preferred to start OACs 1 day after TIA. This shows that physicians are concerned about intracranial bleeding, they may not have enough information and they have confusions about this status. Physicians' NOACs preferences were similar because there are no data in guidelines about NOACs preference.[1]

Most of the physicians preferred propafenone and amiodarone in paroxysmal AF as an antiarrhythmic agent and they chose beta blockers and digoxin for rate control in patients with low ejection fraction. European guideline[1] recommends flecainide and propafenone in patients without significant structural heart diseases and considers beta blockers and digoxin for long term rate control in LVEF <40% of patients. However, amiodarone could easily be found in our country which might be the reason for this preference. If there were more antiarrhythmic agents in our country, the physicians might have had confusions and differences about drug selections.

Study limitations

We did not group physicians according to their specialities and experiences. Perhaps we would have more homogenous responses if we had organized a survey with the same specialty and experience. And also we could not reach more physicians, so it was a limited study.

Conclusion

In this survey, the definitions of valvular and nonvalvular AF, specific patients' managements were heterogeneous among physicians. This survey suggests that explorative data of NOACs phase III trials cannot convince most physicians and they have confusions and believe there is insufficient evidence about subgroup analyzes. Prospective multi-centered large randomized controlled trials focused on specific subgroups as kidney diseases, frail old patients, etc., and specific conditions are needed. Nowadays, the studies of NOACs with subgroups are underway and the results are expected in the world of medicine.

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Conflicts of interest

There are no conflicts of interest.

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Discrepancies Not Only in Physicians, But Also in Atrial Fibrillation Guidelines

Atrial fibrillation (AF) is an established risk factor for a first or recurrent stroke.[1] The advent of direct oral anticoagulants (OACs) has resulted in a choice of therapeutic agents for stroke prevention in patients with AF in addition to Vitamin K antagonists (VKA). Although there are many recommendations of different societies such as American College of Cardiology/American Heart Association/Heart Rhythm Society (AHA/ACC/HRS), European Society of Cardiology (ESC), and Canadian Cardiovascular Society AF guidelines, there are important differences among them. Specifically, major differences can be observed in the nomenclature of OACs, the definition of nonvalvular AF (NVAF), the stroke risk stratification algorithm used to determine criteria for oral anticoagulant therapy, and the role of acetylsalicylic acid (ASA) in stroke prevention in AF.

In this issue of the journal, Sanliap *et al*.[2] published an interesting web-based survey regarding possible discrepancies on perception and management strategies of AF expressed by Turkish physicians.

Various terms have been used to describe the "new" class of OACs. The International Society on Thrombosis on Haemostasis suggests using the term "direct oral anticoagulant [DOAC]" to this treatment that directly inhibits a single target and has clinical properties (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban) based on a web-based survey which includes 16 thrombosis, hemostasis, anticoagulation, and vascular medicine societies from North America and Europe (total 150 participants).[3] However, ESC prefers non-VKA OACs (NOACs) which is currently the main term used by the much larger community of cardiologists.[4]

Beyond the nomenclature, there are important differences in the definition of NVAF. In 2018, the European Heart Rhythm Association suggested a novel classification for NVAF.[5] According to this guide, Evaluated Heart valves, Rheumatic or Artificial (EHRA) categorization is proposed, depending on the type of OAC use in patients with AF. EHRA Type 1 refers to AF patients with valvular heart disease (VHD) needing therapy with a VKA, including in particular moderate–severe mitral stenosis of rheumatic origin and mechanical prosthetic valve replacement. In contrast, EHRA Type 2 VHD refers to VHD patients needing thromboembolic prevention therapy for AF with a VKA or a NOAC, including essentially all other native valvular stenoses and insufficiencies as well as mitral valve repair, bioprosthetic valve replacements, and transaortic valve intervention.

In 2019, update of 2014 AHA/ACC/HRS AF guideline states VHD more narrowly as moderate-to-severe mitral stenosis (any etiology) or mechanical heart valve.[6]

Interestingly, although there are no specific statements about any valve regurgitation in guidelines, Sanliap *et al*.[2] found that 36% of participants evaluated mitral regurgitation as valvular AF.

For stroke risk prediction, guidelines use the CHA_2DS_2-VAS_c score.[6,7] Although the ESC was first to adopt CHA_2DS_2-VAS_c score, in 2016, the ESC guideline modified the criteria of female sex as an independent risk factor, perceiving that "female sex does not appear to increase stroke risk in the absence of other stroke risk factors." In line with the ESC, recent AHA/ACC/HRS guideline changed previous suggestions to female sex, if the only risk factor, does not confer a CHA_2DS_2-VAS_c score of 1. Female sex adds to the score only when another risk factor is present.[6] Both guidelines recommend to use OACs for patients with AF and CHA_2DS_2-VAS_c score of 2 or greater in male or 3 or greater in women (Class 1 recommendation). However, there is a discrepancy between two guidelines to use OAC for patients with AF and CHA_2DS_2-VAS_c score of 1 in male or 2 in women. While the ESC makes a Class 2a recommendation for these groups, according to the recent AHA/ACC/HRS guideline, OAC use might be reasonable (Class 2b recommendation).

The ESC has entirely eliminated ASA from their guidelines in 2016. Similarly, the current AHA/ACC/HRS guideline does not recommend ASA for patients with low CHA_2DS_2-VAS_c score. When OAC is indicated, a preference for DOAC over VKAs is expressed by both AHA/ACC/HRS and ESC (Class 1 recommendation).[6,7]

Sanliap *et al*.[2] reported in their survey that 63% of physicians preferred to use OACs in AF patients with CHA_2DS_2-VAS_c score of 1 in male or 2 in women. In addition, 21% of them prescribed ASA (answers from question 10). Nevertheless, 71% of physicians set CHA_2DS_2-VAS_c score 2 or greater as the limit to start OAC therapy in a female patient with AF (answer from question 17). Because question 10 and 17 interrogated the knowledge of AHA/ACC/HRS and ESC guidelines, respectively, these findings support the discrepancies of them.

Another finding from the survey was 26% of the physicians preferred ASA in older patients. In furtherance, 21% of participants did not prefer to use OAC in geriatric population and concomitant risks (e.g., risk of falling). However, falling risk should not be an exclusion criterion to anticoagulant since

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older patients are at an increased risk of stroke and have been shown to benefit from OAC.[5]

In conclusion, in spite of the small number of participants, this present study represents a nice addition to a growing body of evidence how they were perceived by Turkish physicians. The contemporary management of AF continues to evolve as the new trials and guidelines are published. Because of inadequate findings for specific subgroups/conditions, we need more data from well-designed studies for the potential use of these therapeutic agents in AF.

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Case Report

Persistent Atrial Fibrillation Ablation in a Case of Persistent Left Superior Vena Cava with Absence of the Right Superior Vena Cava

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Abstract

The great majority of atrial fibrillation cases originate from pulmonary vein (PV) triggers; however, non-PV triggers may be the drivers of the arrhythmia, especially in the patients with a persistent left superior vena cava (PLSVC). The presence of a PLSVC may be suggested with a dilated coronary sinus on transesophageal echocardiography during the procedure and may be confirmed with an atrial angiogram, if not known beforehand. Detection and elimination of true trigger site are the most important step for clinical success in such cases.

Keywords: Ablation, atrial fibrillation, persistent left superior vena cava, transesophageal echocardiography

Introduction

On the basis of modern knowledge, pulmonary vein (PV) and non-PV triggers consist of main target in atrial fibrillation (AF) ablation. The role of persistent left superior vena cava (PLSVC) in etiopathogenesis of AF is still sparse. This report presents the reasonable approach to ablation of persistent AF in a case of PLSVC with the absence of right superior vena cava (RSVC).

Case Report

A 58-year-old female with a history of drug refractory symptomatic AF for 6 months was referred to our institution for ablation. Transthoracic echocardiography demonstrated normal cardiac structure, and physical examination was unremarkable. Preablation transesophageal echocardiography (TEE) was deferred because of otherwise relatively low-risk features at the time of ablation (paroxysmal AF substrate, presentation in sinus rhythm, and the patient being on uninterrupted rivaroxaban).

After placement of a duodecapolar coronary sinus catheter, a J-tipped guidewire could not be advanced to the RSVC during fluoroscopically guided transseptal puncture attempt. To allow direct visualization of the transseptal needle tip within the fossa ovalis, we decided to use TEE guidance which demonstrated the absence of RSVC and dilated coronary sinus. To reveal cardiac venous anatomy, an angiogram of the right atrium was performed and confirmed the existence of PLSVC with absent of RSVC [Figure 1a and b].

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Transseptal puncture was performed under the guidance of TEE, and a cryoablation (CA) catheter was inserted into the left superior PV. Before starting CA in the PVs, a duodecapolar catheter was inserted retrograde through the coronary sinus into the PLSVC. Entrance block was observed in PLSVC which confirmed AF was not triggered by PLSVC [Figure 2]. During CA of the left superior PV, AF was first organized and then terminated to sinus rhythm [Figure 3a-c]. Other PVs were isolated using a double-freeze method with each application lasting for 180 s. After completion of PV isolation, the pacing was performed through PLSVC with maximal energy. It verified the existence of exit block. Dormant conduction was not observed and burst pacing attempts did not induce AF with isoproterenol infusion (3.3 μg/min). Postprocedural computed tomography angiography confirmed the existence of PLSVC with the absence of RSVC [Figure 4a and b].

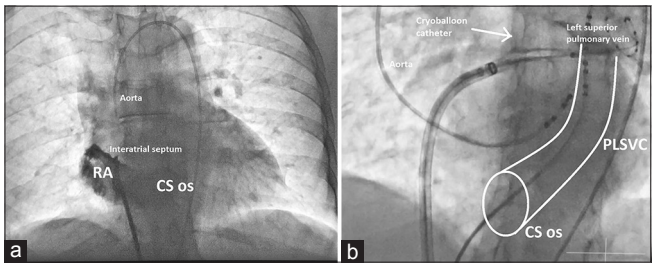


Figure 1: A left anterior oblique fluoroscopic view of the spine. (a) The angiogram of the RA demonstrates absence of a right-sided superior vena cava. (b) A coronary sinus catheter is placed in the PLSVC. The border of CS os and PLSVC was indicated with white lines. CS os: Coronary sinus ostium, PLSVC: Persistent left superior vena cava, RA: Right atrium

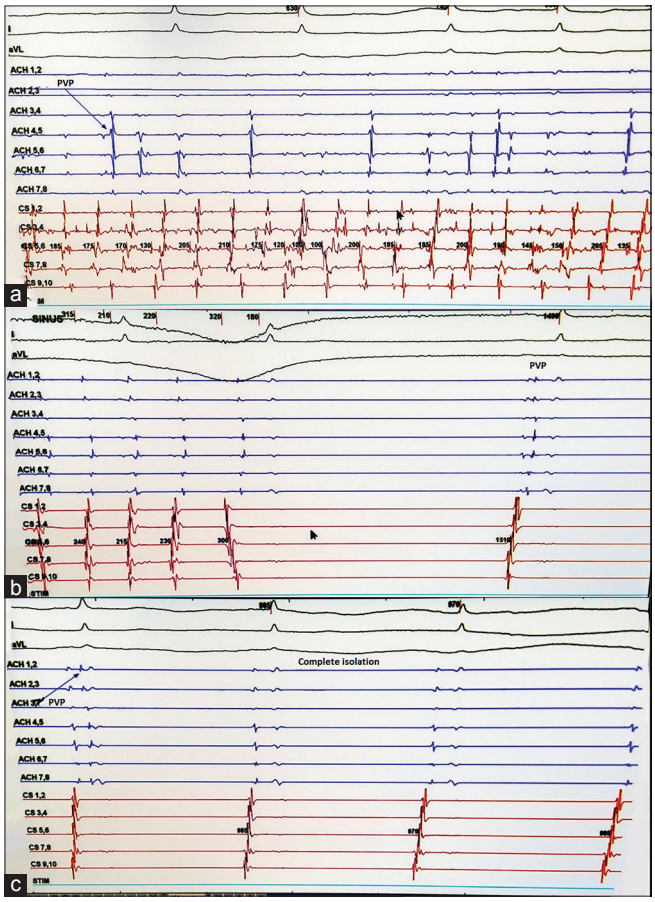


Figure 3: Intracardiac recordings of the left superior pulmonary vein. (a) Atrial fibrillation is seen at the beginning of cryoablation in the left superior pulmonary vein. (b) Atrial fibrillation is organized and terminated while ablation is in progress. Please take care that pulmonary vein potential is still seen in the last beat. (c) Isolation of pulmonary vein is achieved in the second beat

Discussion

The dominant trigger for AF is usually PVs although non-PV foci may explain arrhythmia recurrence in some patients after PV isolation.[1,2] In the presence of PLSVC which may contain remnant muscular and pacemaker tissue carried over from embryonic life, it may contain trigger sites for initiation of AF.[3] Possible electrical connections between PLSVC to the coronary sinus and to the left atrium are considered the main cause of arrhythmogenic properties of PLSVC. Despite these anatomical considerations, we detected an entrance block in PLSVC during AF which confirmed that AF was not triggered by PLSVC in our case. Therefore, we did not perform ablation in PLSVC. If PLSVC was detected the trigger site for AF, focal ablation in trigger site or electrical isolation of PLSVC should be attempted.[3,4]

Although transseptal puncture under fluoroscopic guidance may have a reasonable safety profile in experienced hands, serious

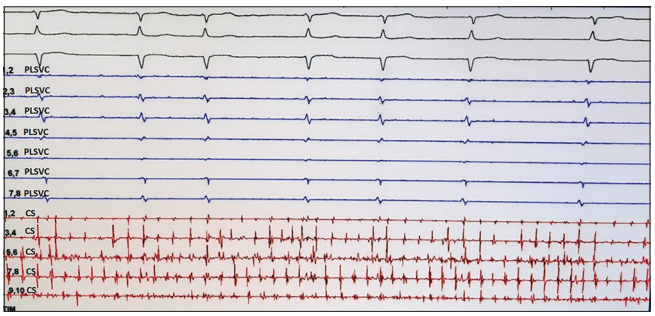


Figure 2: Intracardiac recordings of the PLSVC. There is no atrial electrogram in the left superior vena cava which suggests entrance block. PLSVC: Persistent left superior vena cava

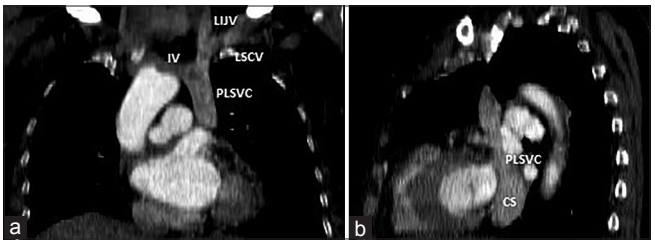


Figure 4: Contrast-enhanced coronal chest computed tomography images. (a and b) The images demonstrate the presence of persistent left superior vena cava and absence of a right-sided superior vena cava. CS: Coronary sinus, IV: Innominate vein, LIJV: Left internal jugular vein, LSCV: Left subclavian vein, PLSVC: Persistent left superior vena cava

complications such as cardiac tamponade (1.31%) or aortic perforation can still occur and can lead to death (0.15%).[5,6] To deal with these possible complications, transseptal puncture should be done under TEE or intracardiac echocardiography guidance. The use of echocardiographic guidance for transseptal puncture does not only enable a safe procedure but also enables puncture site selection within the fossa ovalis according to the expected procedure type (e.g., a more anterior puncture for ablation of an accessory pathway at the mitral annulus or more posterior puncture for ablation of AF). Furthermore, the possibility of safely initiation of anticoagulation before transseptal puncture may be another important advantage of echocardiographic guidance.[7]

As a conclusion, PLSVC is an anomalous structure may cause procedural challenge and additionally may serve as a substrate for AF. Despite, the dominant trigger for AF is usually non-PVs in PLSVC cases; it should be kept in mind to check electrical activity of anomalous PLSVC before attempting empirical ablation.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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Case Report

Large Thrombus on a Prosthetic Aortic Valve Diagnosed on the 1st Postpartum Day

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Abstract

40 years old female with prosthesis aortic valve had developed shortness of breath and consulted to our clinic on the first postpartum day. Her dyspnea was worsened at the last week. She had a history of Bentall operation before 16 years ago, and had a bi-leaflet mechanical prosthetic valve. After detection of pregnancy, her warfarin treatment had switched to enoxaparine 6000 IU subcutaneously for twice a day, continued throughout the pregnancy. Her weight was 62 kg. She did not have any blood test for factor Xa. On physical examination, she has orthopnea, tachypnea (24/min), tachycardia (128 bpm) and hypotension (85/55 mmHg). Electrocardiogram was uneventful with sinus tachycardia of 128 bpm with normal axis. Echocardiography revealed normal left ventricle size with left ventricle hypertrophy, ejection fraction of 60%, reduced motion of prosthetic-valve leaflets and an obstructing mass between the struts. Doppler ultrasonography showed that prosthetic aortic valve has a pressure gradient of 104/59 mmHg. These findings were consistent with prosthetic thrombosis. Moderate aortic regurgitation into the left ventricle was also detected. Transesophageal echocardiography showed 1.4 × 2.3 cm thrombotic material located over leaflets and adjacent to the posterior aortic wall. It was restricting the valve motion. The patient underwent emergency operation immediately. The thrombotic material over mechanical valve was extracted and there was no pathology seen on mechanical valve, graft repaired primarily. Postoperative recovery was fine. No bacteria were detected both direct microscopy and culture.

Keywords: Aortic, day, first, postpartum, thrombus, valve

Introduction

Thrombosis of mechanical prosthetic valve prosthesis in pregnancy is a challenging situation. Here, we present a case who has large thrombus on her prosthetic aortic valve.

Case Report

A 40-year-old female with prosthesis aortic valve had developed shortness of breath and consulted to our clinic on the 1st postpartum day. An elective cesarean delivery with spinal anesthesia was performed at the 37th week of pregnancy of her first child. She had a history of Bentall operation before 16 years ago and had a bileaflet mechanical prosthetic valve (27 mm, St. Jude Medical, Inc., MN, USA). She had no other cardiac risk factors such as hypertension, diabetes, or dyslipidemia. After the detection of pregnancy, her warfarin treatment had switched to enoxaparin 6000 IU subcutaneously for twice a day, continued throughout the pregnancy. Her

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weight was 62 kg. She did not have any blood test for factor Xa. Due to the patient referred from the outer health center, there were no other follow-up data or transthoracic echocardiogram report during pregnancy. Her dyspnea was worsened in the last week. On physical examination, she has orthopnea, tachypnea (24/min), tachycardia (128 bpm), and hypotension (85/55 mmHg). Bilateral lungs were normal on auscultation. No clinical evidence of deep vein thrombosis was present. Other physical examination findings were normal. Electrocardiogram was uneventful with sinus tachycardia of 128 bpm with normal axis. Echocardiography revealed normal left ventricle size with left ventricle hypertrophy, ejection fraction of 60%, reduced motion of prosthetic valve leaflets, and an obstructing mass between the struts. Pulmonary artery pressure was 25 mmHg. Doppler ultrasonography showed that prosthetic aortic valve has a pressure gradient of 104/59 mmHg. These findings were consistent with prosthetic thrombosis. Moderate aortic regurgitation into the left ventricle was also detected. The international normalized ratio (INR) at admission was 1.02 and hemoglobin was 11.2 gr/dL. Transesophageal echocardiography showed 1.4 cm × 2.3 cm thrombotic material located over leaflets and adjacent to the posterior aortic wall [Video 1 and Figure 1]. It was restricting the valve motion. The patient underwent emergency operation immediately. The thrombotic material over mechanical valve was extracted, and there was no pathology seen on mechanical valve, graft repaired primarily. Postoperative recovery was fine. Thrombotic material was sent for microbiological examination. No bacteria were detected both direct microscopy and culture.

Discussion

The patient was a young female with no cardiac risk factors for thrombosis. Long-term enoxaparin medication throughout the pregnancy was chosen for anticoagulation for her prosthetic aortic valve. Despite enoxaparin dose was adequate for her weight, anti-Xa levels were not monitored. The effectiveness of low-molecular-weight heparin (LMWH) did not ensure and thrombosis occurred. We could not describe when thrombus was exactly grow. After delivery with cesarean section, volume depletion has occurred. Her symptoms related to obstructive thrombosis were exacerbated.

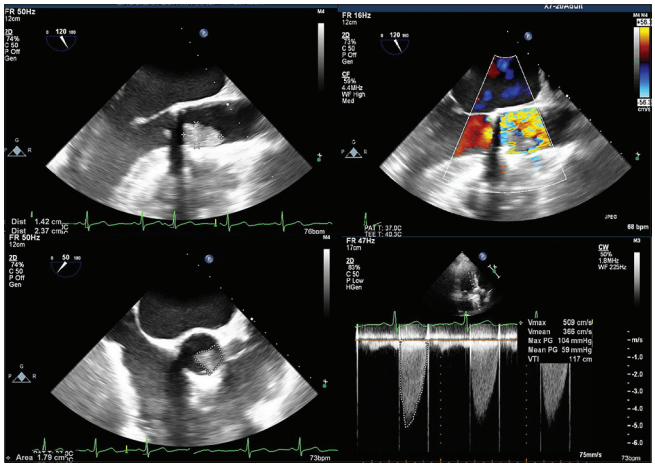


Figure 1: Left upper and lower panel: large thrombus on prosthetic aortic valve was seen; right upper panel: color Doppler showed turbulent aortic flow; and right lower panel: continuous wave Doppler showed severe pressure gradient on the prosthetic aortic valve

Prosthetic valve thrombosis is the most serious thromboembolic complication with high mortality.[1] The bileaflet mechanical, St. Jude Medical, valve prosthesis has a very low complication rate with a thrombosis rate of 0.03% per patient a year.[2,3] The two leaflet pivots of this prosthesis are designed within a "butterfly" recessed in the orifice ring without fixed pivot points. This allows rapid, controlled movement of the leaflets with reduced possibility of thrombus formation.[4] Velocity and turbulent shear stress studies of this mechanical valve prosthesis found that the region adjacent to the pivot mechanism has a combination of high turbulent shear stresses and flow separation.[5] Nevertheless, larger valve size seems to be a risk factor for the late thromboembolic event.[1]

Patients with mechanical heart valve prosthesis should have lifelong anticoagulant drugs to reduce thromboembolic complications. Pregnancy can promote thrombosis of mechanical heart valve prosthesis and embolic events. Hence, effective anticoagulation is obligatory. Vitamin K antagonists (VKA) and unfractionated heparin (UFH)/LMWH have potential side effects. VKA not only has protective effects for prosthetic valve and embolism but also has teratogen for the fetus. UFH/LMWH were safer for the fetus; however, there were some concerns for prosthetic valve and thromboembolism.[6]

Optimal therapy regimen is not well defined; some therapeutic options were defined. At the first trimester, dose adjusted LMWH or dose UFH can be used. VKAs are associated with embryopathy, spontaneous abortion, premature birth, fetal bleeding, and fetal death at the first trimester.[7] Negative effects of warfarin to the fetus seem like dose dependent.[8,9] Although it is known that the patients who require ≤5 mg/day warfarin (or acenocoumarol <2 mg/day, phenprocoumon <3 mg/day) could be used,[10] recent studies concerning the safety of low-dose warfarin are controversial.[11] On the other hand, LMWH and UFH do not cross the placenta; therefore, substitution of VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy.[11] In the second and third trimester, VKA therapy can be used. In peripartum period, LMWH or UFH should be used. Vaginal delivery while the mother is on VKA is contraindicated because of the risk of fetal intracranial bleeding.[12] Despite all three regimens have hemorrhagic complications, the incidence is lower with VKAs.[9] In the present case, the patient used enoxaparin throughout the pregnancy. Although this was an acceptable option in former studies,[6] it is now advised to switch LMWH/UFH therapy to VKA after the first trimester because of the risk of prosthesis valve thrombosis.[11]

If LMWH was chosen for anticoagulation in the patient with prosthetic heart valve and pregnancy, plasma anti-Xa levels

should be higher than 0.6 IU/ml before the next dose of LWMH. After 4–6 h of injection, anti-Xa levels should be in the range of 1.0–1.2 U/ml for mitral and right-sided valves or in the range of 0.8–1.2 U/ml for aortic valves.[11] This regimen should not be used if anti-Xa levels could not be monitored.[7] In our patient, unfortunately, LMWH activity did not monitor with anti-Xa levels.

The management of mechanical prosthetic valve thrombosis is high risk, whatever the option is taken. Anticoagulation, fibrinolysis, or emergency surgery can be chosen. Obstructive prosthetic valve thrombosis in critically ill patients without a contraindication to surgery should undergo emergency valve replacement. Fibrinolysis may be considered if the surgery is at high risk but carries a risk of bleeding and thromboembolism.[10] If the patient is not critically ill and has a history for inadequate anticoagulation, an intravenous UFH plus aspirin can be administrated before emergency surgery or fibrinolysis decision. In nonobstructive thrombus, if thromboembolism exists with thrombus larger than 10 mm, surgery or fibrinolysis should be performed. The patients with smaller thrombus should receive anticoagulant therapy. Persistence of smaller thrombus with a second thromboembolism should be managed with surgery or fibrinolysis. If thromboembolism not exists, large thrombus (>10 mm) which resistant to anticoagulation should receive surgery/fibrinolysis. Small thrombus should receive anticoagulant therapy and follow-up unless the patient has thromboembolism.[11] Management of mechanical valve thrombosis in pregnancy is a more challenging situation. A team comprising a cardiologist, cardiovascular surgeon, obstetrician, and perinatologist should decide which strategy is the best for the patient.

Conclusion

This case illustrates the need for closer monitoring of the anticoagulation treatment in patients with large-size prostheses after the replacement of the aortic valve, even if the mechanical valve was uneventful for many years. In case of suspected valve thrombosis, early diagnosis is recommended, and emergency operation is indicated in patients with critical condition.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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