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CONTEMPORARY REVIEW

Exploring Refractoriness as an Adjunctive Electrical Biomarker for Staging of Atrial Fibrillation

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ABSTRACT: Patients diagnosed with the same subtype of atrial fibrillation according to our current classification system may differ in symptom severity, severity of the arrhythmogenic substrate, and response to antiarrhythmic therapy. Hence, there is a need for an electrical biomarker as an indicator of the arrhythmogenic substrate underlying atrial fibrillation enabling patient-tailored therapy. The aim of this review is to investigate whether atrial refractoriness, a well-known electrophysiological parameter that is affected by electrical remodeling, can be used as an electrical biomarker of the arrhythmogenic substrate underlying atrial fibrillation. We discuss methodologies of atrial effective refractory period assessment, identify which changes in refractoriness-related parameters reflect different degrees of electrical remodeling, and explore whether these parameters can be used to predict clinical outcomes.

Key Words: atrial fibrillation ■ biomarker ■ electrophysiology ■ refractory period

Patients diagnosed with the same subtype of atrial fibrillation (AF) according to our current classification system may differ in symptom severity, severity of the arrhythmogenic substrate, and response to antiarrhythmic therapy.[1] Paradoxally, patients with *different* AF subtypes may have similar severities of the arrhythmogenic substrates. Hence, there is a need for an electrical biomarker as an indicator of the arrhythmogenic substrate underlying AF. The availability of such an electrical biomarker enables staging of AF and will improve patient-tailored therapy.

A well-known electrophysiological parameter that is affected by AF-induced electrical remodeling is the atrial effective refractory period (AERP). AERP shortens in response to accelerated activation frequencies, so-called rate adaptation of refractoriness. After deceleration, AERP prolongs again but even after sufficient time for recovery, AERP in patients with a history of AF remains relatively shorter. This indicates that AF inflicts permanent damage on cardiomyocytes' rate adaptation capacities. In addition, electrical remodeling can manifest heterogeneously throughout the atria, and subsequent dispersion of refractoriness is widely acknowledged as a key player in the pathophysiology of both onset and maintenance of AF.

If refractoriness is affected gradually as the arrhythmogenic substrate progresses, it could potentially be used as a biomarker for AF.

The aim of this review is to investigate whether atrial refractoriness can be used as an electrical biomarker of the arrhythmogenic substrate underlying AF. We discuss methodologies of AERP assessment, identify which changes in refractoriness-related parameters reflect different degrees of electrical remodeling, and explore whether these parameters can be used to predict clinical outcomes.

RATE DEPENDENCY OF AERP

As mentioned above, AERP is rate dependent and adapts to the preceding cycle length. Duration of AERP

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Nonstandard Abbreviations and Acronyms

AERP	atrial effective refractory period
APD	action potential duration
APD90	action potential duration at 90% of repolarization
BCL	basic cycle length
PAF	paroxysmal atrial fibrillation
peAF	persistent atrial fibrillation
PV	pulmonary veins
PVI	pulmonary vein isolation

is directly related to the action potential duration (APD).[2] Acute increase in activation rate during rapid stimulation or tachyarrhythmia causes intracellular Ca^{2+} overload in the cardiomyocytes.[3] This triggers downregulation of L-type Ca^{2+} channels and upregulation of slow rectifier K^+ currents, resulting in faster repolarization and thus AERP and APD shortening, so-called rate adaptation.[4,5]

Rate adaptation was first demonstrated in 20 patients without structural heart disease in whom episodes of pacing-induced AF shortened AERP at basic cycle lengths (BCLs) of 500 and 300 ms from 216±17 to 191±30 ms (P<0.0001) and 206±23 to 175±30 ms (P<0.0001), respectively.[6] After a mean period of 8.4±0.3 minutes, AERPs were restored to pre-AF values. Rate adaptation occurs immediately after cycle length shortening[2] and is progressive when the tachycardia persists. In the goat model of AF, the AERP shortened from 131±11 to 106±17 ms after 24 hours of induced AF but shortened even further to 70±12 ms after 43±34 days of pacing.[7] The shortest possible AERP is unknown, yet in both experimental and clinical studies, a minimal AERP of 50 to 60 ms is commonly applied.[8,9] However, the rationale for this cutoff value remains unclear, as there are no reports on assessment of the minimum duration of refractoriness.

Beat-to-beat changes in APD during steady-state pacing (APD alternans), related to cyclic fluctuations in intracellular Ca^{2+} concentrations, were related to onset of AF in humans.[10–12] Varying APD morphology was most prominent in the early repolarization phase, and recently involvement of changes in total outward K^+ currents was demonstrated as well in human left atria (LA). During simulation of an action potential, using a mathematical model of human atrial cardiomyocytes, replacement of K^+ channels type Kv4.3 by slower recovering type Kv1.4 (more fetal or undifferentiated variant), as occurs because of mechanical or endocrinological stress, increased occurrence of APD alternans.[13] APD alternans occurs only at rapid pacing frequencies; in 12 patients with persistent atrial fibrillation (peAF), 13 patients with paroxysmal atrial fibrillation (PAF), and 8 controls, APD alternans started at cycle lengths of 316±99, 266±19, and 177±16 ms, respectively (P=0.02).[11]

"GOLD STANDARD" REFRACTORINESS MEASUREMENTS

In general, refractoriness is determined by extrastimuli (S2) pacing during electrophysiological studies and defined as the longest S1–S2 interval that fails to propagate a response. Pacing stimuli open voltage-gated Na^+ channels, enabling Na^+ influx, resulting in depolarization.[14] The relation between stimulus strength and AERP was examined in 25 patients with a history of syncope and atrial or ventricular tachyarrhythmias; shortening of AERP attributable to increasing stimulus strength occurred progressively up to stimuli of relatively 5.3±1.7 mA at a BCL of 600 ms and 5.9±1.5 mA at a BCL of 300 ms (P=NS). At this point, refractoriness had been reached and AERP did not shorten further as stimulus strength was increased up to 10 mA.[15] Thus, there is an inverse relationship between AERP and stimulation current. Therefore, AERP can be reliably compared between patients only when similar stimulus strengths are applied during pacing.

Reliability of the premature stimulus methodology for AERP determination in nonuniform anisotropic cardiac tissue is questionable, as previously discussed by Spach et al.[16] The AERP is commonly defined as the interval between pacing stimuli rather than the interval between atrial activations measured at the recording site. Therefore, frequency-dependent conduction delays during premature stimulation arising between the pacing and recording site result in apparently shorter AERPs. Distance between the pacing and recording electrode should therefore also be taken into account when comparing AERP between different atrial sites, but this is rarely reported.

Another parameter that has been used to estimate AERP is time to reach 90% of the action potential repolarization (APD90). The reliability of APD90 measurements remains debatable, as when both AERP and ADP90 are determined in the same individual, substantial differences were observed.[10] Comparing APD90 to AERP at a BCL of 600 ms, for example, 226±16 ms versus 211±24 ms in patients with persistent AF (peAF, N=18), 250±35 ms versus 233±29 ms in patients with PAF (N=14), and 258±25 ms versus 229±19 ms in control subjects (N=9), respectively, were measured. Hence, these observations indicate that the APD90 is not a suitable substitute for AERP. Validity of monophasic action potential catheters are debated as well, as they are prone to movement artefacts.[17]

For both methodologies of measuring refractoriness, using progressively faster steady-state pacing may result in different AERPs or APDs than the extrastimulus methodology,[18] as refractoriness has more time to adjust. Moreover, reports on the occurrence of APD alternans indicate that in some patients, repolarization may be temporally irregular even during constant stimulation rate.[19]

INDIRECT DETERMINATION OF AERP

As prior experimental and clinical studies demonstrated that the minimum or fifth percentile of the interval histogram corresponded to the AERP determined during extrastimuli protocols, these values have been widely accepted as a surrogate measure for AERP. In an isolated perfused canine model (N=8), high-density (256 sites) epicardial AF recordings with a duration of 10 seconds proved sufficient to estimate AERP by using the minimum AF cycle length.[20] Likewise, in patients with PAF (N=25), the fifth percentile approximated AERP when calculated from at least 100 consecutive fibrillation intervals measured endovascular at the high right atrium (RA), low RA, coronary sinus, or oval fossa.[21]

Excitation of cardiomyocytes directly after the AERP is mandatory to derive the AERP from an interval histogram. However, as reflected by the large variation in fibrillation intervals, cardiomyocytes are probably rarely excited at the exact moment that refractoriness ends, and as a consequence, an excitable gap is often present.[22] Also, when the fibrillation rate is low or regular, longer recordings may be required to estimate the AERP.

Other ways to determine AERP during AF include slow fixed-rate pacing and entrainment. Duytschaever et al[8] used an experimental goat model to compare various methodologies including an extrastimuli protocol (AERP, 70±12 ms); entrainment (77±17 ms; R^2 correlation coefficient=0.88; $P<0.01$), fixed-rate pacing (71±17 ms; $R^2=0.84$; $P<0.01$) and the fifth percentile AF cycle length (77±12 ms, $R^2=90$, $P<0.01$) and found that all approaches correlated well with the extrastimuli "gold standard."

Even though these results look promising, it is important to realize that the shortest interval measured probably represents the *shortest possible* AERP of local cardiomyocytes. The refractory period changes over time, as fibrillation intervals vary from beat to beat.

REFRACTORINESS IN NONREMODELED ATRIA

Table 1 provides an overview of experimental and clinical studies assessing refractoriness in nonremodeled hearts.[2,6,7,10,21,23–28] In clinical studies, at BCLs of 400, 500, and 600 ms, AERP ranges from 213±35 to 266±37 ms, 215±29 to 277±42 ms, and from 227±20 to 291±53 ms, respectively. This table also shows that despite the fact that humans and animals share comparable cardiac dimensions, absolute AERPs may still differ.

For example, at a BCL of 400 ms, AERP was 150±8 ms in canine RA and 146±19 ms in the LA and RA of goats,[7] compared with AERPs ranging from 213±35 to 266±37 ms (BCL, 400 ms) in human nonremodeled atria. Extrapolation of refractoriness measures in animal models to humans should thus be done with caution.

Official reference values for "normal" refractoriness are scarce. As previously discussed, only Daoud et al[6] assessed refractoriness in nonremodeled human atria. AERP was determined in the RA of 20 patients without a history of AF (stimulus: 3× diastolic threshold; mean threshold, 0.7±0.2 mA). At BCLs of 500 and 350 ms, AERPs were 216±17 and 206±23 ms, respectively.

Various factors may influence AERP assessed during electrophysiology studies such as magnitude of decrements in extrastimuli and cardio-active medication like antiarrhythmic drugs or anesthetics.[23] In addition, refractoriness is dependent on the measuring site, and AERPs may vary from region to region.[29,30] Finally, hysteresis of refractoriness measurements may also cause discrepancy in study results, as it has been reported that incremental extrastimuli lead to longer AERPs or APDs than decremental extrastimuli in a canine model.[31,32] However, as studies using both approaches to determine AERP in human atria are not available from the literature, head-to-head comparison of incremental and decremental extrastimuli protocols is not possible.

SPATIAL DISTRIBUTION OF AERP IN NONREMODELED ATRIA

In adult canines, APD in the RA shortened as distance to the sinus node increased.[33] In another study, AERPs measured using basket catheters in the lower part of the canine RA were indeed longer compared with the high part of the RA (BCL 400 ms, 111±23 ms versus 94±24 ms; $P<0.01$; BCL 300 ms, 104±20 ms versus 96±23 ms; $P<0.01$). AERP was also longer at the smooth posteroseptal RA than at the trabeculated RA free wall (102±25 ms versus 97±17 ms; $P<0.05$) at a BCL of 300 ms, suggesting that AERP may be dependent of atrial wall morphology as well.[34] However, at a BCL of 400 ms AERP did not differ between the smooth and trabeculated wall.

Satoh and Zipes[35] found longer AERPs in the thinner medial RA free wall compared with the thicker lateral (terminal crest) region (BCL,300 ms; AERP, 149±12 ms

Table 1. Summary of Studies Investigating AERP in Nonremodeled Atria

Year of Publication, First Author	Subjects, N	Incremental or Decremental	Stimulus Strength	Location	BCL (ms)	AERP (ms)	Comment
Experimental studies							
1995, Wijffels[7]	Goats, 12	Incremental, 2-ms steps	4× threshold	RA, LA	Max	117±12	Small study population
					200	131±11	
					250	145±13	
1995, Morillo[24]	Dogs, 10	Decremental, 10-ms steps	2×DT	RA	300	147±11	Small study population
					400	150±8	
1995, Wijffels[7]	Goats, 12	Incremental, 2-ms steps	4× threshold	RA, LA	400	146±19	Small study population
Clinical studies							
2001, Brundel[23]	13	…	…	LAA, RAA	250	184±5	Small study population, anesthesia
					300	224±16	
1996, Daoud[6]	20	Incremental, 5-ms steps	3× threshold, mean 0.7±0.2 mA	RA (2 sites)	350	206±23	
1995, Capucci[21]	10	Decremental, 1-ms steps	2.5×DT	RA, CS, or LA	400	266±37	Small study population
2001, Brundel[23]	13	…	…	LAA, RAA	400	252±34	Anesthesia
1987, Soni[2]	11	Decremental, steps: -	3 mA	RA	436±81	225±29	BCL not standardized
1995, Capucci[21]	10	Decremental, 1-ms steps	2.5×DT	RA, CS, or LA	500	267±42	Small study population
1996, Daoud[6]	20	Incremental, 5-ms steps	3× threshold, mean 0.7±0.2 mA	RA (2 sites)	500	216±17	
2001, Brundel[23]	13	…	…	LAA, RAA	500	277±42	Anesthetics, sternotomy
2010, Centurion[25]	62	Decremental, 10-ms steps	2×DT	RA, CS	500	215±29	
1995, Capucci[21]	10	Decremental, 1-ms steps	2.5×DT	RA, CS or LA	600	281±35	Small study population
1998, Chen[27]	20	Incremental, 10-ms steps	2×DT	RA	600	211±26	
2001, Brundel[23]	13	…	…	LAA, RAA	600	291±53	Anesthetics
2002, Kim[10]	9	…	…	RA (6 sites)	600	227±20	Small study population
2016, Lee[28]	1308	Decremental, 10-ms steps	2× threshold	RA	600 (in 93%)	233±31	BCL not standardized
1985, Alboni[26]	20	Decremental, 10-ms steps	2×DT	RA	680±68	211±27	BCL not standardized
1987, Soni[2]	11	Decremental, steps: -	3 mA	RA	709±80	250±38	BCL not standardized

"-" indicates no details provided; AERP, atrial effective refractory period; BCL, basic drive cycle length; CS, coronary sinus; DT, diastolic threshold; LA, left atrium; LAA, left atrial appendage; RA, right atrium; and RAA, right atrial appendage.

versus 133±8 ms; $P<0.01$) in 9 anesthetized open-chest dogs, suggesting that atrial refractoriness is related to wall thickness. Local variation in refractoriness were, however, not found in the RA of newborn dogs, indicating that regional AERP differences develop during aging.[16]

AERP distribution was described in more detailed by Vollmann et al.[36] In 6 goats, AERPs were assessed at 11 epicardial regions, including the RA and LA free wall (array, 1×1.5 cm, 12 electrodes) and Bachmann's bundle area (array, 10×1.3 cm, 56 electrodes). AERP was longest at mid-Bachmann's bundle (AERP, 185±6 ms) and shortest at the LA free wall (AERP, 141±5 ms; $P<0.001$). Other experimental studies also found that AERPs in the LA are shorter.[8,29,37–39]

Measurements of AERP at a BCL of 120 ms combined with tissue analysis in 9 mice atria demonstrated that LA AERP was shorter than the RA AERP (16.9±0.9 ms versus 19.8±1 ms; $P<0.05$) and that both total outward and inward rectifier K current density were increased in the LA suggestive of enhanced capacity for rate adaptation.[39]

Clinical studies have reported regional differences in AERP, but it is usually not measured at a high-resolution scale, or sites at which AERP is the shortest or longest are not described.

Remarkably, in few clinical studies, regional differences in AERPs were compared between the nonremodeled LA and RA. In 22 patients without AF, AERP was longer in the distal coronary sinus (BCL, 500 ms; AERP, 244±30 ms) than in the RA (219±20 ms; $P<0.01$).[40] This difference in AERP between the RA and coronary sinus was also confirmed by other clinical studies.[30,37]

These observations contrast with many experimental studies assessing regional differences in AERP, as mentioned above. However, patients in whom AF was repetitively induced were excluded, which may have caused a selection bias. There is also no evidence that AERPs in the LA and distal coronary sinus are comparable.

Whether electrical remodeling results in regional differences in AERP remains unclear. In goats, 4 weeks of atrial pacing (BCL, 150 ms) shortened AERPs, but it did not result in enhancement of regional AERP differences that were already present during sinus rhythm.[36]

In 29 patients with a history of PAF, AERP at the pulmonary veins (PVs) was shorter than both the LA and the RA (PV, 174±62 ms; LA, 254±30 ms; RA, 221±29 ms; $P=0.0001$).[41] In a similar patient population, AERP was shorter at the distal PV than the PV-LA junction (PAF, N=48; AERP, 177±43 ms versus 222±30 ms, respectively; $P<0.0001$).[42] Unfortunately, spatial distribution of AERP between PV and LA has so far not been described in nonremodeled atria, so whether electrical remodeling affected regional differences in AERP is unknown.

IMPACT OF AF ON REFRACTORINESS

In Table 2, clinical studies reporting on AERP measured in patients with different subtypes of AF and control patients are summarized.[21,23,25,43-48] In general, patients with a history of AF have shorter AERPs than patients without AF.[21,23,25,30,47–49] In patients with PAF, at a BCL of 600 ms, AERP varied between 193±23 and 310±51 ms. This variation may be, as discussed above, attributable to many variables affecting AERP measurements, but it may also reflect heterogeneity in the AF substrates.

Interestingly, several investigators have reported shorter AERP in patients with PAF compared with patients with peAF,[10] which is in contrast with the assumption that persistence of AF progressively shortens refractoriness. A possible explanation for this observation may be the increased prevalence of LA dilatation in patients with peAF, which prolongs AERP.[27,30,47,49]

In absence of atrial dilatation, AERP is shorter in patients with peAF than in patients with PAF.[47] When AERPs were longer in patients with peAF, this could be explained by atrial dilatation. Although tachycardia initially causes upscaling of K^+ ion channel expression and shortening of repolarization, atrial dilatation leads to permanent reduction in both Ca^{2+} and K^+ channel expression, resulting in prolonged AERP.[4,50,51] Therefore, because of extensive electrical or structural remodelling in peAF, "normalisation" of AERP occurred and diminished differences between patients with PAF and patients with peAF.[10,30,49]

FAILURE OF RATE ADAPTATION

Rate adaptation is a dynamic process reflected by rate adaptation curves, demonstrating the AERPs at different BCLs. Persistent shortening of AERP despite cycle length prolongation is referred to as failure of rate adaptation and causes attenuation of the rate adaptation curve. This phenomenon has been described in isolated human atrial cells of dilated RA appendages,[52] RA canine cells after fast rate activation,[4,53] and several clinical studies.[23,54–56]

In a detailed protocol, steepness of rate adaptation curves derived from the LA and RA appendage (BCL range, 250–600 ms) were compared between anesthetized patients with peAF (N=13), PAF (N=16), and no history of AF (N=13) before coronary artery bypass surgery.[23] The slope of the rate adaptation curve was less steep in patients with peAF compared with patients with PAF and controls (peAF, 87±57; PAF, 109±38; no AF, 138±33; $P<0.05$). This reduction in rate adaptation capacity correlated with a progressive decrease in protein expression of L-type Ca^{2+} channel, Kv4.3, Kv1.5, hERG, minK, and Kir3.1 in both LA and RA appendages. These results indicate that decreasing steepness of the curve may relate to progressive ion channel dysfunction and thus to progression of the AF substrate.

Likewise, APD restitution, illustrated by fitted curves of APD90 plotted against preceding diastolic intervals, was less steep in 13 patients with peAF than in 27 patients with PAF in the LA and PV area.[19] Patients in the PAF group showed a maximum APD restitution slope of 1.5±0.4, whereas in peAF group steepness was 0.7±0.2 ($P<0.001$). In the RA, however, slope was

Table 2. Summary of AERP Comparisons Between Different AF Subtypes

Year of Publication, First Author	Subjects, N	Protocol	Recording Location	BCL (ms)	AERP (ms), Controls	AERP (ms), PAF	AERP (ms), peAF
1991, Kumagai[48]	12 peAF 12 controls	Decremental, 10-ms steps	HRA, CS	…	238±23		215±1*
1995, Capucci[21]	25 PAF, 10 controls	Decremental, 1-ms steps	HRA, CS	600	231±36	193±2*	
				500	231±32	190±2*	
				400	234±34	178±4*	
1998, Pandozi[44]	14 peAF	Decremental, 2-ms steps	RA (mean of 5 sites)	700			207±19
				600			203±18
				500			198±17
				400			191±15
				300			180±15
1999, Kamalvand[43]	13 peAF, 8 controls	Decremental, 10-ms steps,	RAA	600	265		210*
			MLRA	600	228		215
			RAA	400	270		200*
			MLRA	400	218		216
2000, Osaka[46]	10 peAF, 10 controls	Decremental, 5-ms steps, 2×	RA	600	247±25		224±13
			RA	400	233±25		215±1*
2001, Brundel[23]	13 controls, 13 PAF, 16 peAF	…	RAA, LAA	600	291±53	222±1*	208±3*
				500	277±42	224±2*	207±2*
				400	252±34	216±2*	203±2*
				300	224±16	202±20*	189±24*
				250	184±5	185±19	172±17
2010, Centurion[25]	58 PAF, 62 controls	Decremental, 10-ms steps	RAA	500	215±29	208±2*	
2013, Uhm[47]	343 PAF, 140 peAF	Decremental, 1-ms steps	HRA	500		233±29	231±27
			LRA	500		229±31	228±27
			PCS	500		251±3†	236±3†
			DCS	500		258±4†	237±3†
			Mean of all locations	500		243±27†	233±2†
2016, Nguyen[45]	28 PAF	Incremental, 2-ms steps	HRA	600		310±51	
			PCS	600		289±36	
			DCS	600		289±50	
			Left PV	600		257±62	
			Right PV	600		265±62	
			Mean of all locations	600		283±30	

AERP indicates atrial effective refractory period; BCL, basic drive cycle length; DCS, distal coronary sinus; HRA, high right atrium; LA, left atrium; LRA, low right atrium; MLRA, midlateral right atrial wall; PAF, paroxysmal atrial fibrillation; PCS, proximal coronary sinus; peAF, persistent atrial fibrillation; PV, pulmonary vein; RA, right atrium; and RAS, right atrial septum.

*Significantly different from controls.

†Significantly different between types of AF.

1.3±0.4 in patients with PAF and 1.5±0.3 in patients with peAF (*P*=NS). In contrast, Kim et al[10] also measured APD90 using a monophasic action potential catheter at 6 locations in the RA and compared APD restitution between patients with peAF, patients with PAF, and patients without AF. The mean slope was steeper

in patients with PAF (1.1±0.4) and peAF (1.4±0.3) than in control patients (0.5±0.3, $P<0.01$), but mutual differences between AF subtypes were not significant.

The explanation for the contradicting results is unknown. However, there were differences in measuring sites, pacing protocols (eg, extrastimuli or dynamic steady-state pacing[10]), and analysis methodologies, each of which affect APD and APD restitution slope steepness. In addition, in both rate adaptation curves and APD restitution curves, a plateau phase was reached. Therefore, the range of BCLs or diastolic intervals along which mean curve steepness is calculated may determine mean adaptation slope as well.

However, in all of the above-mentioned studies, it was not reported whether AF was induced or present before surgery. This may be of importance, as failure of rate adaptation restores after restoration of sinus rhythm. Yu et al[55] compared 19 patients with peAF (>6 months) to 20 age-matched controls without a history of AF or atrial flutter. In the peAF group, rate adaptation curves constructed from AERPs at the RA appendage and distal coronary sinus 30 minutes after cardioversion were less steep (RA: slope, 0.049±0.024 versus 0.074±0.016; distal coronary sinus: slope, 0.098±0.042 versus 0.162±0.040, respectively; both $P<0.01$). After 4 days of sinus rhythm, however, rate-adaptation curves no longer differed from the curves obtained from the control group (0.066±0.101 versus 0.162±0.040; $P>0.05$), indicating that tachycardia-induced impairment of rate adaptation can be transient in nature. Additional studies are necessary to establish whether the slope of rate adaptation can be used to distinguish between different AF subtypes, taking into account duration of sinus rhythm and AF episodes.

INTERREGIONAL VERSUS INTRAREGIONAL DISPERSION OF REFRACTORINESS

Heterogeneous manifestation of electrical remodeling throughout the atria causes increased dispersion of refractoriness, which is generally accepted as one of the key players in AF onset and maintenance. As a consequence, for example, unidirectional conduction block of short-coupled ectopic beats caused by localized areas of prolonged refractoriness may initiate reentry.

There are generally 2 ways to measure "dispersion of refractoriness." In many studies, dispersion of AERP is defined as the maximum difference in AERP between varying atrial regions—in other words, interregional differences. For the sake of clarity, studies in which dispersion is defined as the difference between minimum and maximum AERPs from varying regions are referred to as studying *interregional dispersion*. When mapping data with a high spatial resolution (including multiple AERPs per anatomic region) is used and intraregional differences are defined by a mathematical measure of variation, this will be referred to as *intraregional dispersion*.

INTERREGIONAL DISPERSION RELATED TO AF SUBTYPES

Several studies have compared interregional dispersion of AERP between patients with and without AF. In each of these studies, a different set of recording sites was used, composed of only RA or both RA and LA recording sites, hampering comparison of study outcomes.

Interregional AERP dispersion between the high, mid, and lower RA wall was increased in 23 patients with PAF compared with 20 patients without AF (45±28 versus 34±13; $P<0.05$).[57] However, increased interregional AERP dispersion between the RA appendage and mid RA was demonstrated in 8 patients without AF compared with 13 patients with peAF (dispersion, 54 ms versus 18 ms, respectively; $P<0.01$).[58] There were also no differences in interregional AERP dispersion when 6 measuring sites throughout the RA were compared between patients with peAF (N=18), PAF (N=14), and no history of AF (N=9). The average amounts of interregional dispersion in AERP were 32.4±30.3 ms (peAF), 41.7±27.4 ms (PAF), and 32.7±19.2 ms (no AF), respectively (*P* values not provided).[10]

Likewise, when 3 RA and LA sites were combined, there was no difference in interregional dispersion between patients with peAF (N=11), PAF (N=8), and no history of AF (N=10).[30] Other studies demonstrated in a similar patient population that interregional dispersion of AERP was increased in patients with AF compared with patients without AF (peAF, N=18; PAF, N=22; no AF, N=19, corresponding to dispersions of 44.0±18.5, 49.3±29.9 and 23.5±14.1 ms, respectively; ANOVA, $P<0.01$).[49]

In a larger cohort of patients with AF (PAF, N=343; peAF, N=140), interregional dispersion in AERP between 4 LA and RA sites was 56.3±34.8 ms in PAF versus 44.6±25.0 in peAF ($P<0.001$).[47] Patients were excluded when AERP could not be determined because of AF induction. These excluded patients may be especially interesting as the arrhythmogenic substrate may be more pronounced, but it was not reported whether they were included in the peAF or PAF group.

In conclusion, evidence is conflicting with respect to interregional dispersion in AERP. Although interregional dispersion appears increased in patients with PAF

compared with patients without a history of AF, there is no evidence that interregional AERP dispersion is enhanced in patients with peAF compared with patients with PAF.

AERP in peAF was less dispersed than in patients with PAF and even than in patients without AF.[10,43,47] This observation is not in line with the assumption that increased dispersion of AERP is associated with a more elaborate arrhythmogenic substrate in patients with peAF. It is unclear why reduced interregional dispersion was found in these patients with more progressive stages of remodeling. General shortening of the AERP may *reduce* regional differences. This was previously reported by Wijffels et al[7] who used an epicardial array containing 6 electrodes (interelectrode distance, 6–10 mm) to determine interregional dispersion of AERP between the RA appendage and LA appendage in 5 goats before AF induction, 24 and 48 hours after induction of sustained AF. Regional differences in AERP were 14, 22, 20, and 16 ms at BCLs of 400, 300, 250, and 200 ms, respectively, compared with 8, 8, 6, and 8 ms after 48 hours of AF (*P* value not provided). Although they described AF up to only 48 hours after induction, the same principle may apply to a general shortening of AERP in patients with peAF compared with patients with PAF.

Whether differences in interregional dispersion were mainly caused by shorter minimum or longer maximum AERPs was not reported in any of the clinical studies reporting on interregional dispersion of AERP. Also, as dispersion in refractoriness is already demonstrated in closely adjacent RA sites,[10] the relevance of randomly chosen, widely spaced atrial sites for the assessment of interregional dispersion is questionable. Increased spatial density of AERP measurements leading to a more detailed assessment of AERP distribution throughout the atria (intraregional dispersion) may be required to elucidate these remaining questions.

INTRAREGIONAL DISPERSION RELATED TO AF SUBTYPES

Pacing in ex vivo rabbit atrial myocardium revealed that a minimum difference of 11 to 16 ms in AERP between adjacent electrodes (interelectrode distance unknown) was associated with local conduction block during premature extrastimuli.[59] Dispersion of refractoriness will thus lead to a frequency-dependent, scattered, and variable pattern of lines of conduction block, creating a substrate for the onset and maintenance of reentry circuits.

The relation between activation rate and dispersion in AERPs was first demonstrated in an experimental canine model by Fareh et al.[29] Dispersion of refractoriness was defined as the coefficient of variation of AERPs (standard deviation/mean AERP) at 73 sites on the epicardium (interelectrode distance not provided). The coefficient increased from 13.5% to 21.7% (*P* value not provided) during 24 hours of fixed-rate pacing (BCL, 150 ms) and was associated with increased susceptibility to AF induction (r=0.81; P<0.001). In addition, Li et al[58] discovered a 3-fold increase in intraregional dispersion of refractoriness in patients with PAF (N=21) compared with patients with acutely induced AF (N=12), defining dispersion as variance (squared SD) among the fifth percentile AF cycle length of 5 to 16 sites in RA and LA (AERP variance, 717±469 ms; acutely induced AF, 299±123 ms, respectively; P<0.05). The observed differences could mainly be attributed to shorter fifth percentile in the PAF group.

These studies support the hypothesis that increased intraregional dispersion of refractoriness causes increased susceptibility to AF. Unfortunately, no other studies have yet reported on the dispersion of refractoriness in patients with peAF. Whether intraregional dispersion is best represented by these methodologies and whether they can be used to distinguish between different degrees of the arrhythmogenic substrate is yet to be discovered.

PREDICTION OF AF ONSET

In 734 patients with atrioventricular nodal reentrant tachycardia or a concealed bypass tract (N=1308; age, 44±16 years), spontaneous onset of AF within 12 years was enhanced if AERP at the high RA was >280 ms (BCL, 600 ms in 93%; hazard ratio adjusted for age, 2.08; P =0.041).[28] This seems to contrast with the association between short AERPs and AF. However, patients with AERP ≥280 ms (n=34; 10.3%) also had larger LA size (41±6 mm versus 36±6 mm; P<0.001), which, as previously discussed, prolongs AERP. When an AERP of 280 ms is compared with AERPs measured in nonremodeled RA of nonanesthetized patients (Table 1), 280 ms indeed seem disproportionally long.

Interregional dispersion in AERP of >76 ms between high RA, low RA, and distal and proximal coronary sinus was related to AF onset within 24 months after ablation of an atrioventricular bypass or slow atrioventricular node pathway in 845 patients (area under the curve, 0.896; 95% CI, 0.833–0.959; P<0.05).[60] Sensitivity and specificity were not provided, nor was the stimulation protocol. Although prior atrial tachycardia was an exclusion criterion, the authors mention AF recurrence rather than onset, suggesting that AF had occurred before.

PREDICTION OF SUSCEPTIBILITY TO AF INDUCTION

AERP has also been used to predict susceptibility to artificial AF induction. In most studies, it was

demonstrated that enhanced susceptibility to AF induction was associated with shorter AERPs. In both isolated and in vivo canine atria, shortening of AERP was associated with increased inducibility of sustained AF.[61,62] Pharmacologically induced AERP shortening increased susceptibility to AF induction in dogs,[63] whereas AERP prolongation reduced AF inducibility in swine.[64]

In clinical studies, there was no relation between AERP and AF inducibility in patients with or without structural heart disease and with supraventricular tachycardia, when defining successful induction as AF lasting either >10 seconds (N=50)[65] or >5 minutes (N=44).[66,67] A possible explanation for the disparate outcomes is that AERP by itself does not reflect the arrhythmogenic substrate. In a canine model, increased intraregional dispersion of AERP, defined as covariance among 96 epicardial sites, was an independent risk factor for AF induction (stepwise multilinear regression; $P<0.0001$), whereas ERP alone was not.[29]

Interregional dispersion was related to successful AF induction both in experimental and clinical studies but could not be used to identify patients at risk of AF persistence.[62,67] In a canine model (anesthesized, hypothermic, vagal stimulation), interregional dispersion between the sinus node area, the low posterior RA, and the distal coronary sinus was increased in dogs susceptible to AF induction (59±24 ms versus 29±18 ms; $P<0.001$).[62] Similarly, in patients with a history of PAF, interregional dispersion between the high RA, low RA, interatrial septum, and proximal and distal coronary sinus was larger in the AF inducible group (N=22; 105±78 ms) than in the noninducibility group (N=11; 49±20 ms; $P<0.05$).[68] In a follow-up study, however, interregional dispersion did not differ between patients in whom induced AF terminated spontaneously or persisted.[67]

The occurrence of APD alternans may also predict susceptibility to AF induction. In a small study of 12 patients with peAF, 13 patients with PAF, and 8 patients without a history of AF, APD alternans preceded all successful AF inductions.[11] In cases where APD alternans had disappeared because of loss of capture, AF was noninducible. In addition, in 19 patients without structural heart disease, especially discordant APD alternans was related to AF inducibility.[69] Discordant alternans was evoked in 13 of 19 (46%) patients and followed by AF initiation in 8 of them ($P=0.012$).

It is unclear, however, whether susceptibility to AF induction relates to AF onset or recurrence in real life. Moreover, induction protocols vary considerably, jeopardizing validity and reproducibility of study results, as susceptibility to AF induction is strongly dependent on, for example, the number of induction attempts and stimulus strengths.[66]

PREDICTION OF EARLY POSTOPERATIVE AF

In 56 patients admitted for coronary artery bypass grafting (AF, N=18; no AF, N=38), interregional dispersion of refractoriness (high RA, posterolateral RA, distal coronary sinus) was an independent predictor of postoperative AF incidence (odds ratio, 1.29; 95% CI, 1.12–1.47; $P<0.001$).[70] It was not reported which patient group showed more interregional dispersion.

PREDICTION OF SUCCESSFUL ABLATIVE THERAPY

In 67 patients with both an accessory pathway and AF, the relation between interregional dispersion and recurrence rate was used to predict which patients benefit from PV isolation (PVI) concomitant to ablation of the accessory pathway. Concomitant PVI was performed in 29 patients. Interregional dispersion of >75 ms was related to AF recurrence within 36 months (sensitivity, 70%; specificity, 92%; $P=0.003$). If dispersion was >75 ms (PVI, N=9; no PVI, N=11), concomitant PVI resulted in lower recurrence rates (2 [18.2%]) than pathway ablation alone (7 [77.8%]; $P=0.012$). When dispersion was <75 ms, no difference in recurrence rates was established between the PVI (N=18) and non-PVI groups (N=25).[71] The way in which patients were assigned to the PVI or non-PVI group is not described; however, interregional dispersion was similar in both groups. These results suggest that regional differences in refractoriness may aid in selecting patients who will benefit most from additional PVI ablation therapy, but additional research will have to be performed to confirm and solidify these outcomes.

CURRENT APPLICABILITY OF REFRACTORINESS AS AN ELECTRICAL BIOMARKER

AF-induced electrical remodeling is related to AERP shortening, dispersion of refractoriness, and attenuated slopes of AERP–rate adaptation curves. However, none of the reviewed parameters seem to have a strict linear relation with the arrhythmogenic substrate underlying AF. Although differences in refractoriness have been demonstrated between patients with different AF subtypes, considerable overlap in AERPs is observed. Construction of, for instance, receiver operating characteristic curves to further examine the predictive value of AF may be useful.

In many studies, environmental factors influencing AERP are not fully measured or documented. Those

factors may include the pacing protocol (measuring site, stimulus strength, BCL), data processing (eg, choosing the appropriate blanking period for determination of local activation time), atrial dilatation, stimulation of the autonomous nervous system, cardio-active medication (usage of antiarrhythmic medication, anesthetics), and phases of electrical (reverse) remodeling (such as time since AF onset/induction, time since conversion to sinus rhythm). Therefore, standardized pacing protocols and elaborate documentation are required to accurately measure AERP and compare study outcomes.

There are several hurdles to overcome in order to establish whether AERP is a suitable biomarker for staging of AF. For example, as there are most likely both interregional and intraregional differences in AERPs, a detailed map of refractoriness is essential to gain insight into dispersion in refractoriness in both nonremodeled and remodeled atria.

Determination of AERP during AF, however, as is required for patients in whom cardioversion cannot be accomplished, may be even more problematic. As discussed above, the reliability of the minimum or 5th percentile of the AF cycle length histogram as a reflection of AERP is questionable. In addition, the AERP changes from beat to beat because of variability in preceding fibrillation intervals.

Another patient group in whom AERP may not have been determined accurately so far includes patients who are susceptible to AF induction. They are often excluded from analysis when no AERP can be determined because of repetitive AF induction. This could have resulted in distortion of study results, as refractoriness especially in these patients may be altered. Using incremental instead of decremental extrastimuli protocols may reduce this problem, as there will be no need for repetitive electrical cardioversion and restarting of the pacing sequence.

At present, interregional dispersion has been studied more frequently than intraregional dispersion of AERP, which does not seem to reflect the arrhythmogenic substrate adequately and is therefore unsuitable as a biomarker. Research into the prognostic value of AERP-derived parameters is limited and needs further investigation.

In the future, pairing refractoriness with additional electrical biomarkers may be considered as well, as AERP is not the only factor that influences susceptibility to AF. Whereas electrical remodeling appears to play a key role in the initiation of AF, additional structural remodeling has proven to be crucial for persistence of the tachyarrhythmia. Progressive wavelength shortening was demonstrated in a canine model after rapid pacing (BCL, 150 ms)[24] and in goats with artificially sustained AF,[7] increasing susceptibility to AF induction and enhancing spatiotemporal disorganization of waves in persistent AF. This occurred a considerable period after AERP had reached a new steady state, increasing stability of AF. This indicated that electrical remodeling alone may not cover the full extent of the arrhythmogenic substrate.

AF persistence may depend on the combination of electrical (AERP shortening) and structural remodeling (such as reduced conduction velocity attributable to, eg, fibrosis or nonuniform anisotropy) rather than AERP alone.[72] Therefore, other dynamic electrical characteristics such as conduction velocity may also be suitable as a biomarker.

ARTICLE INFORMATION

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