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STATE-OF-THE-ART REVIEW

The Blinding Period Following Ablation Therapy for Atrial Fibrillation

Proarrhythmic and Antiarrhythmic Pathophysiological Mechanisms

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ABSTRACT

Atrial fibrillation (AF) causes heart failure, ischemic strokes, and poor quality of life. The number of patients with AF is estimated to increase to 18 million in Europe in 2050. Pharmacological therapy does not cure AF in all patients. Ablative pulmonary vein isolation is recommended for patients with drug-resistant symptomatic paroxysmal AF but is successful in only about 60%. In patients in whom ablative therapy is successful on the long term, recurrence of AF may occur in the first weeks to months after pulmonary vein ablation. The early recurrence (or delayed cure) of AF is not understood but forms the basis for the generally accepted 3-month blinding (or blanking) period after ablation therapy, which is not included in the evaluation of the eventual success rate of the procedures. The underlying pathophysiological processes responsible for early recurrence and the delayed cure are unknown. The implicit assumption of the blinding period is that the AF mechanism in this period is different from the ablation-targeted AF mechanism (ectopy from the pulmonary veins). In this review, we evaluate the temporary and long-lasting pro- and antiarrhythmic effects of each of the pathophysiological processes and interventions (necrosis, ischemia, oxidative stress, edema, inflammation, autonomic nervous activity, tissue repair, mechanical remodeling, and use of antiarrhythmic drugs) occurring in the blinding period that can modulate AF mechanisms. We propose that stretch-reducing ablation scar is a permanent antiarrhythmic mechanism that develops during the blinding period and is the reason for delayed cure. (J Am Coll Cardiol EP 2021;7:416–30) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans (1). The number of patients with AF is estimated to increase to 18 million in Europe only in 2050 (2). AF is associated with increased mortality and increased risk of heart failure and stroke as well as poorer quality of life compared with the general population (3–5). Therefore, the symptomatic treatment and cure of AF are timely medical priorities.

When pharmacological treatment fails to terminate AF, cardioversion or ablation therapy can be applied. The expert consensus group on AF ablation recommends pulmonary vein isolation (PVI) by ablation therapy in the case of drug-resistant symptomatic paroxysmal AF (subsequent episodes of AF that spontaneously terminate in <1 week) (6). Recently, a randomized trial in untreated paroxysmal AF patients appoints PVI to be superior to antiarrhythmic drug (AAD) treatment in preventing AF (7). During both catheter-based and surgical PVI, ablation lesions are created in the junctions between the pulmonary veins (PVs) and the left atrium (LA) to prevent conduction

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HIGHLIGHTS

- Early AF recurrence during the blinding period after ablation is associated with long-term therapy failure.
- Temporary proarrhythmic factors may be culprits of early recurrence.
- Development of a permanent antiarrhythmic effect by scar rigidification may cause delayed cure.
- Unblinding the blinding period allows insight in AF mechanisms that can improve therapy success.

of spontaneous premature beats from the PV myocardium to LA. However, ablation therapy does not lead to cure of AF in all patients with paroxysmal AF. A meta-analysis of 13 studies concluded that 59% of AF patients are arrhythmia free at 5-year follow-up after a single PVI (8).

In the first weeks to months after PVI, AF can recur even when the patient may be free of AF on the longer term (delayed cure) (9). Therefore, the expert consensus group recommends to measure the success of an ablation therapy from 3 months after the procedure onward (6). This period is termed the blinding or blanking period and is now widely adopted in both clinical routine and clinical trials. As a result, a second ablation in a patient with AF recurrence within the blinding period (early recurrence) is not routinely done, because an episode of AF within the blinding period is considered to be an isolated occurrence and not necessarily related to the dominant AF mechanism.

The underlying pathophysiological processes responsible for early recurrence and the delayed cure are unknown. On the one hand, early recurrence is considered the consequence of ablation-induced proarrhythmic factors that are limited to the time frame of the blinding period (6). On the other hand, a delayed cure may also be the cause of an antiarrhythmic effect that develops in the course of the blinding period (**Figure 1**) and that is not necessarily related to electrical isolation of the PV. A potential confounding influence is played by the use of AADs during the blinding period, as they may paradoxically act as a possible proarrhythmic factor. AADs are usually discontinued after the 3-month period, and this may unmask the antiarrhythmic effect of the ablation procedure.

We surmise that by understanding the combined pathophysiological processes that follow ablation, we can ameliorate our insight into ablation success or the lack thereof and thereby improve the techniques to achieve higher long-term success rates of AF ablation therapy. In this review, we will discuss the short-term and long-term pathophysiological processes following ablation therapy in the blinding period and their influence on arrhythmogenesis.

ABBREVIATIONS AND ACRONYMS

AAD = antiarrhythmic drug
AF = atrial fibrillation
CRP = C-reactive protein
GP = ganglionated plexus
HRV = heart rate variability
LA = left atrium
MMP = matrix metalloproteinase
NGF = nerve growth factor
PV = pulmonary vein
PVI = pulmonary vein isolation
ROS = reactive oxygen species
TGF = transforming growth factor
TNF = tumor necrosis factor

THE BLINDING PERIOD

In 2002, Oral et al. (10) observed that 31% of patients with AF recurrence within the first 2 weeks after PVI had no further symptoms at 3- to 4-month follow-up. Because delayed cure is observed in 15% to 49% of patients with early recurrence (11–15), ablation success is therefore most often assessed after a 3-month blinding period (15–18) (**Central Illustration**).

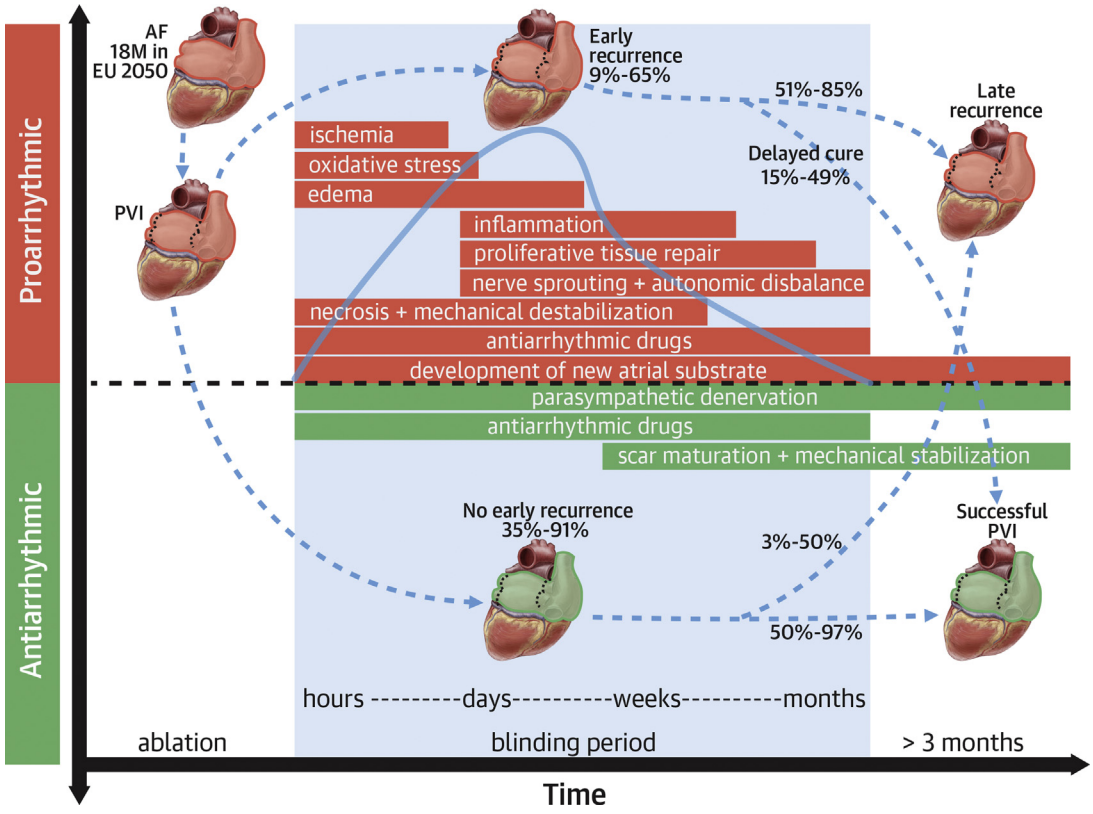
The incidence of early AF recurrence during the 3-month blinding period following PVI ranges from 9 to 65% (11–15,19–25). Joshi et al. (23) described that 54% of patients have early recurrence within week 1 to 2 following ablation therapy, after which the percentage drops to 38% in weeks 2 to 4 and to 24% in weeks 4 to 6. The first episode of early recurrence occurs within month 1 of the blinding period in 81% to 91% of patients with early recurrence (14,15). This emphasizes the dynamic nature of the blinding period.

EARLY RECURRENCE AND ABLATION SUCCESS. Several multivariate statistical analyses show that early recurrence is an independent predictor of AF recurrence after the blinding period (late recurrence) (14,19,21,22,26). Therefore, contrary to what has been suggested, the AF occurrence and maybe even the AF mechanisms during the 2 periods appear to be related.

The timing of early recurrence plays a role in prediction of late recurrence (12,25,27). Success rates of PVI progressively drop the later early recurrence occurs during the blinding period (**Table 1**). **Table 1** shows that the incidence of delayed cure varies between the studies. The applied rhythm monitoring technique may have had an effect.

The time dependence between early and late recurrence indicates that a continuous atrial and PV modification takes place in the early months following ablation. Indeed, the number of premature atrial complexes decreases during the 3-month blinding period (both in patients with and without late recurrence) (28). In summary, arrhythmogenesis during the blinding period is a dynamic phenomenon.

CENTRAL ILLUSTRATION **Early Recurrence of AF and Ablation-Induced Pathophysiological Processes and Interventions During the Blinding Period**



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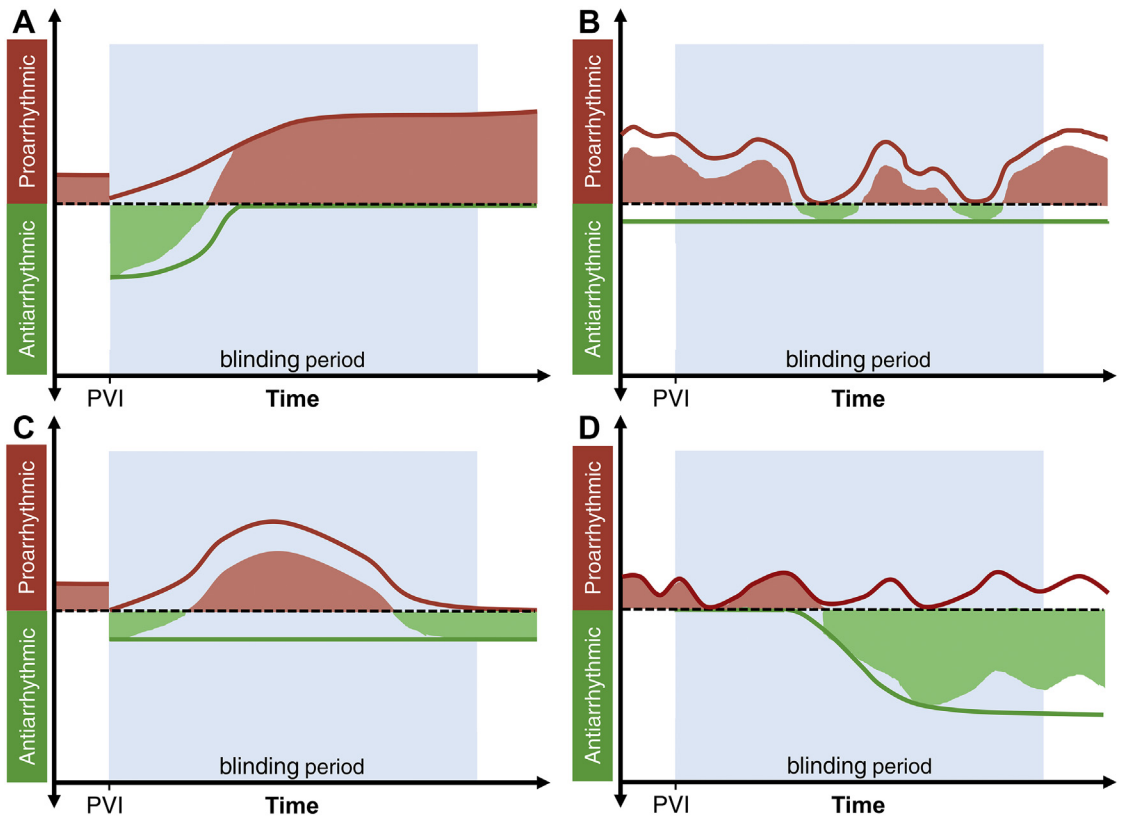
Early recurrence of atrial fibrillation (AF) is common during the 3-month blinding period after pulmonary vein isolation (PVI) ablation and may result in either a successful ablation (delayed cure) or in late recurrence of AF. The PVI ablation procedure induces pathophysiological processes and interventions with both proarrhythmic and antiarrhythmic effects that have different limitations in time.

ARRHYTHMOGENESIS DURING THE BLINDING PERIOD. The observation that early recurrence can be associated with late ablation success may be based on similarity in underlying early and late arrhythmogenic mechanisms (**Figures 1A and 1B**). A new arrhythmogenic substrate may develop at any moment after ablation. Also, electrical reconnection between the PV and LA myocardium is considered a cause of permanent ablation failure, justifying a new PVI procedure (29). However, ablation success also occurs in patients with PV reconnection (30-33). Therefore, the prerequisite of complete electrical isolation to obtain therapy success, and also the role of PV reconnection in early recurrence, can be questioned.

Alternatively, on the one hand, early recurrence without late recurrence may represent a transient and potentially reversible proarrhythmic effect of ablation therapy or the result of stopping AADs (**Figure 1C**). On the other hand, early recurrence may indicate a continuation of the preexisting initial AF mechanisms, and the delayed cure may occur after the "late" development of a permanent ablation-caused antiarrhythmic effect (**Figure 1D**).

Presence of concomitant disease in the patient prior AF ablation may contribute to the arrhythmogenesis during the blinding period. Indeed, structural heart disease (20,22,34) and hypertension (14) are risk factors for early recurrence of AF during the blinding period. Also, enlarged LA (14,22,26,34) indicating progressive AF and higher age (22) increase the risk of early recurrence. These factors are, however, not likely to change during the blinding period and therefore present a factor of permanent influence.

FIGURE 1 **The Possible Explanations for Delayed Cure and Late Recurrence in the Setting of Early Recurrence of AF**



(A) Early recurrence results in either late recurrence or delayed cure after the blinding period. Early recurrence associated with late recurrence may be the result of the combination of the development of a permanent proarrhythmic factor (e.g., new atrial fibrillation [AF] substrate) and an antiarrhythmic factor (e.g., pulmonary vein isolation [PVI]) limited to the blinding period. **(B)** Alternatively, the antiarrhythmic effect of PVI is absent, and the early and late recurrence are a continuum of the preexisting AF, upon which comorbidities exert continuous and dynamical proarrhythmic (and possible antiarrhythmic) effects. Delayed cure can be the result of **(C)** a proarrhythmic factor limited to the blinding period (e.g., inflammation, antiarrhythmic drugs) or **(D)** the development of a permanent antiarrhythmic factor during the blinding period (e.g., stretch-reducing ablation scar). In this latter case, early recurrence is due to preexisting AF. **Shading** indicates the sum of factors.

The PVI procedure induces pathophysiological processes that may influence arrhythmogenesis and thereby early recurrence and delayed cure. The processes and their effect on post-PVI arrhythmias are reviewed subsequently in the chronology by which they appear following PVI. The complexities of interaction of pro- and antiarrhythmic factors are depicted in **Figure 2**. Predictors of early recurrence and the possible underlying mechanisms are displayed in **Table 2**.

PATHOPHYSIOLOGICAL PROCESSES

SHORT-TERM PROCESSES (HOURS TO DAYS). Necrosis. Energy by radiofrequency, cryo, or other sources is delivered at the myocardium with the purpose of interrupting the conduction between the PV and LA myocardium. As a result, coagulative necrosis appears in the myocardium in close contact with the ablation catheter (35). Indeed, troponin marks cardiomyocyte-specific necrosis, and its plasma concentration after ablation therapy correlates with the amount of delivered energy and therefore likely with the size of the lesion (36,37). Troponin concentration peaks at day 1 post-ablation (37–41), and an elevated troponin concentration after ablation is an independent predictor of early recurrence within the first 3 days of the blinding period (37) but not of late recurrence (37,40,42,43). However, Yoshida et al. (44) observed a lower PVI-induced troponin elevation in persistent AF patients with enlarged LA and recurrence at 2 months than in similar patients without

TABLE 1 The Timing of Early Recurrence of AF After Ablation and the Association With Delayed Cure

Early Recurrence	First Author (Ref. #)	N	Rhythm Monitoring	Delayed Cure
Days 0–3	Koyama et al. (27)	45	24-h Holter ECG week 2, months 1, 2, and 3	76%
Weeks 1–2	Oral et al. (10)	39	ECG if symptom complaint	31%
Weeks 1–2	Joshi et al. (23)	39	External loop recorder for 3 months	51%
Days 4–30	Koyama et al. (27)	27	24-h Holter ECG week 2, months 1, 2, and 3	30%
Month 1	Willems et al. (25)	53	Weekly ECG; transtelephonic recording	63%
Month 1	Themistoclakis et al. (14)	417	48-h Holter ECG at months 1 and 3; daily transtelephonic recording	66%
Weeks 1–6	Mugnai et al. (12)	9	24-h Holter ECG at months 1 and 3; telephone calls	100%
Month 2	Willems et al. (25)	44	Weekly ECG; transtelephonic recording	36%
Month 2	Themistoclakis et al. (14)	51	48-h Holter ECG at months 1 and 3; daily transtelephonic recording	31%
Weeks 6–12	Mugnai et al. (12)	5	24-h Holter ECG at months 1 and 3; telephone calls	0%
Month 3	Willems et al. (25)	82	Weekly ECG; transtelephonic recording	8%
Month 3	Themistoclakis et al. (14)	46	48-h Holter ECG at months 1 and 3; daily transtelephonic recording	2%

ECG = electrocardiogram.

recurrence. This can reflect that ablation led to a relatively smaller loss of myocardium and thereby a conservation of more electrical mass in patients with recurrence than patients without recurrence.

In summary, troponin concentration in the ablation setting indicates the extent of necrotic atrial tissue that ultimately influences both the total electrical mass and the structural remodeling in form of scar formation. Also, noncontracting necrotic myocardium causes abnormal mechanics of the adjacent vital myocardium as observed in the setting of ventricular myocardial infarction (45–48). Because altered myocardial mechanics is proarrhythmic (see the following sections), the ablation-induced troponin plasma rise can be an indicative of the degree of mechanical destabilization and thereby arrhythmogenesis after ablation before scar maturation.

Ischemia. Direct artery trauma, thromboembolism, heat-induced collagen shrinkage, and coronary spasm are consequences of radiofrequency energy delivery that result in atrial perfusion changes and subsequently atrial ischemia (49). Indeed, hemorrhage and thrombosis are observed histologically within and in proximity to recent radiofrequency lesions (35,50,51). Because ischemia exerts proarrhythmic changes in the atria (52–54), early recurrence during the blinding period may be ischemia dependent (55). This is supported by the observation that acute atrial myocardial infarction is associated with new onset of AF in humans (56). Also, acute and 8 days of chronic ischemia in right atria increase AF inducibility in dogs (52,53). Depending on the duration of coronary ligation, atrial ischemia causes either a prolongation (5-h ischemia) (52) or shortening (15-min ischemia) (54) of the atrial refractory period in dogs.

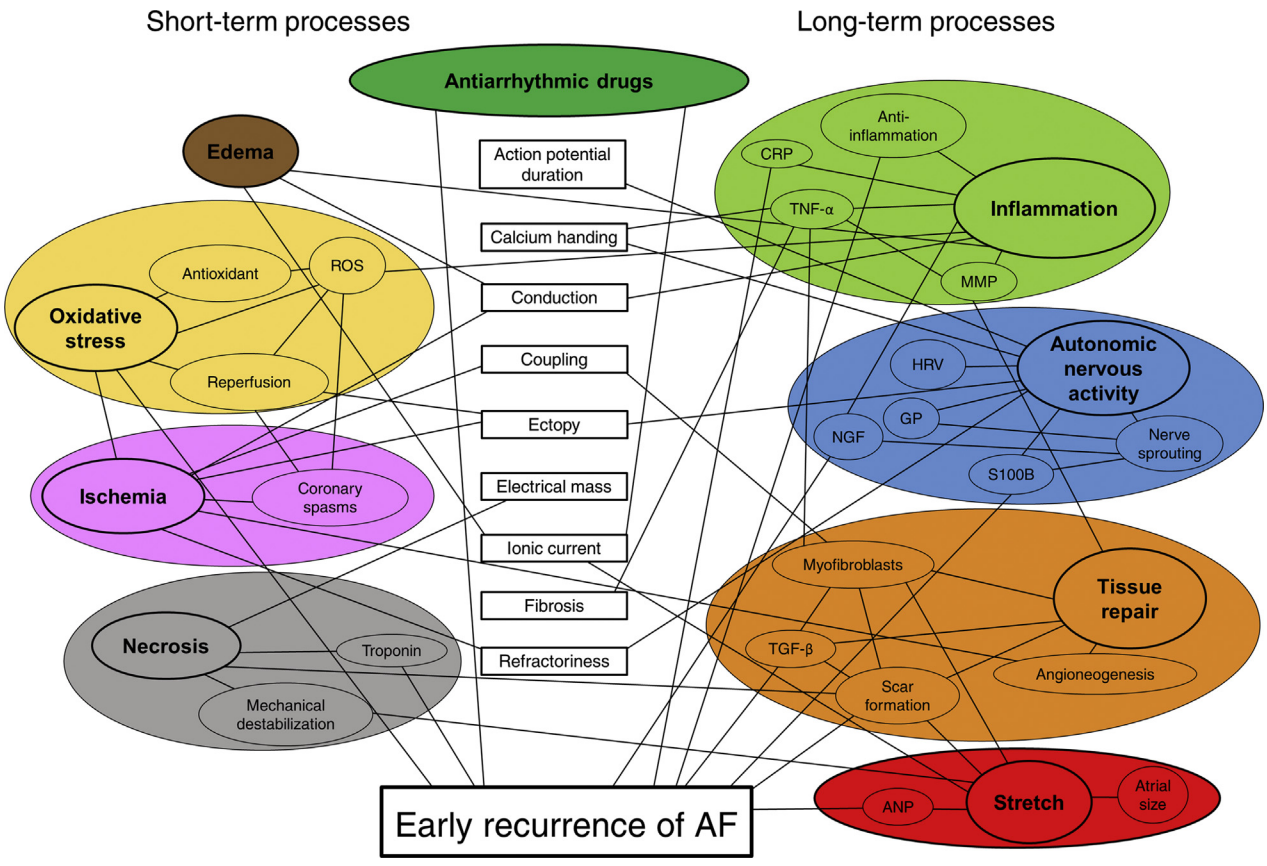
Moreover, the ablated tissue is still electrically coupled to the surviving tissue, leading to depolarization of the latter (57). This will cause conduction slowing and action potential changes (57,58). Intercellular uncoupling occurs within hours after ischemic ventricular myocardial infarction and is attributed to closure of the gap junctions (59). Partial or heterogeneous intercellular uncoupling acts proarrhythmic, whereas complete or uniform uncoupling ceases arrhythmogenesis (59,60). Therefore, acute atrial ischemia in the setting of PVI is likely to contribute to an immediate proarrhythmic state.

A decrease in the diameter of arteries due to collagen denaturation occurs within seconds after heat stress and continues to evolve within the first hours (61,62). Later, the coronary artery media is replaced with extracellular matrix in 2-week-old canine ventricular radiofrequency lesions (63). Therefore, permanent coronary artery injury due to direct trauma and narrowing after ablation may lead to chronic atrial ischemia and thereby to continuation of a proarrhythmic setting. Indeed, concomitant atrial coronary artery disease is a predictor of AF after ventricular myocardial infarction (64).

Finally, complete arterial occlusion results in myocardial necrosis that exceeds the ablated area, subsequently causing fibrosis that interdigitates healthy tissue (57). As a consequence, conduction will follow tortuous pathways facilitating re-entrant activation (65,66).

In summary, it remains unknown whether atrial ischemia due to ablation therapy is causative of early recurrence as proposed. Alternatively, recovery from chronic ischemia may concur with the blinding period because histological preparations demonstrate

FIGURE 2 **Ablation-Induced Pathophysiological Factors Present Within the Blinding Period, Their Interaction, and Effect on Arrhythmogenesis**



The ablation procedure induces short- and long-term pathophysiological processes and interventions that alter atrial electrophysiology. **Colors** indicate manuscript sections (subtitle in **bold**) in which the pathophysiological factors are discussed. AF = atrial fibrillation; ANP = atrial natriuretic peptide; CRP = C-reactive protein; GP = ganglionated plexus; HRV = heart rate variability; MMP = matrix metalloproteinase; NGF = nerve growth factor; ROS = reactive oxygen species; TGF-β = transforming growth factor beta; TNF-α = tumor necrosis factor alpha.

angiogenesis near ablation lesions from week 2 onward (51,67,68). PR-segment depression or elevation on the electrocardiogram, as a marker of atrial ischemia and its evolution during the blinding period after PVI, can be informative but solid information is lacking.

Oxidative stress. Reactive oxygen species (ROS) are generated in injured myocardium during both ischemia and reperfusion following cardiac surgery and are associated with postoperative AF (69). Indeed, atrial oxidative stress due to ROS production is increased in AF patients compared with control patients in sinus rhythm (70). Therefore, oxidative stress plays a possible role in AF arrhythmogenesis after ablation. Decreased plasma levels of markers of oxidative stress 3 months after PVI correlate with less AF burden after the blinding period (71). Also, immediate ablation-induced (6 h to 2 days) elevation of oxidative stress-related myeloperoxidase predicts early recurrence during week 1 post-ablation but not recurrence at 12-month follow-up (72). However, the marker is not specific of oxidative stress because it also marks inflammation (73).

Coronary spasms responsive to nitric oxide donors occur during atrial radiofrequency ablation (74,75) and are thought to be due to autonomic nervous activity (49). Coronary spasms can induce acute atrial ischemia and subsequently arrhythmias. However, also the abolition of the coronary spasms may induce a transient phase of arrhythmias through reperfusion injury by oxidative stress. Indeed, early and delayed afterdepolarizations are observed during hypoxia in superfused rabbit PVs, whereas accelerated spontaneous potentials (burst firing) only occur during the

reoxygenation (76). The latter was suppressed by pharmacological reduction of ROS generation (76).

The specific effect of oxidative stress on early recurrence after ablation therapy is unknown. A preliminary study has shown that oral vitamin C decreases early recurrence within week 1 after cardioversion in persistent AF patients (77). Thus, pharmacological treatment with antioxidants, nitric oxide donors or statins in the blinding period may reduce early recurrence.

Edema. Edema is observed in the atrium immediately and 1 day after delivery of ablative energy (78–83) and is resorbed by 1 or 3 months in humans (80,84,85). Thus, myocardial edema in the setting of ablation is a transient phenomenon. It has been suggested that edema is responsible for early recurrence (86), potentially through alterations in electrical conduction and transmembrane ionic currents or swelling of cardiomyocytes (87–94).

When the interstitial volume is augmented and the cardiomyocyte volume is diminished by addition of mannitol to the Langendorff perfusion solution, the ventricular conduction is slowed, as a result of increased intermembrane spacing near the gap junctions (87,88). In contrast, others observe an increase of ventricular conduction velocity upon increased interstitial volume by arterial perfusion of a blood solution containing the colloid dextran (89). Observations on atrial myocardium are lacking.

An increase in cell volume activates swelling-activated ion channels (90). Swelling of canine atrial myocytes depolarizes the resting membrane by an outward chloride current (a net inward current) (91). Also, aquaporins in the cell membrane are permeable to water and may influence electrophysiology indirectly via swelling or shrinking of cardiomyocytes and the consequent changes in ionic concentrations in the intracellular and extracellular fluids (90).

Thus, ablation-caused edema is resolved within weeks, and the possible electrophysiological changes occur in the early blinding period. Edema is likely to generate proarrhythmic changes.

LONG-TERM PROCESSES (WEEKS TO MONTHS).

Inflammation. Inflammation drives AF arrhythmogenesis via electrophysiological and structural atrial remodeling (95) and is suggested to cause early AF recurrence after atrial ablation (6,86,96). Indeed, the ablation procedure induces a local and systemic inflammatory response (82,97). A systemic inflammatory state in humans without AF caused by strenuous exercise is associated with reversible P-wave prolongation on the electrocardiogram without LA volume changes (98). These observations are consistent with atrial conduction slowing. Similarly, local atrial inflammation in dogs due to sterile pericarditis or atriotomy causes heterogeneous conduction slowing and increase in AF vulnerability and AF duration, which is prevented by intravenous steroid therapy (73,99).

Local inflammation. Localized cellular release of danger-associated molecules and degraded extracellular matrix caused by the ablative energy initiate the inflammatory response (95). Neutrophils are present in human ventricular myocardium with a 1-day old radiofrequency lesion (100), although these are not yet present in a porcine model of a 2-h ventricular radiofrequency lesion (50). The inflammatory infiltration primarily consists of neutrophils in 1-week-old right atrial ablation lesions (82), whereas macrophages, multinucleated giant cells, and lymphocytes infiltrate the borders of 2-week-old atrial ablation lesions (51,67). Later, the inflammatory infiltrate predominantly is constituted by lymphocytes (4 weeks) (82). After 8 and 12 weeks, the infiltrate is resorbed (82). Thus, an inflammatory infiltrate is present in the atrial myocardium in this first half of the blinding period.

Systemic inflammatory markers and ablation. Compatible with the appearance of a local inflammatory infiltrate, the plasma concentration of C-reactive protein (CRP), a marker of systemic inflammation, increases after atrial ablation and reaches a peak on days 2 to 3 after the procedure and stays elevated until day 7 (37,72,97). Increased CRP level is also observed in pigs following LA catheterization without radiofrequency delivery, as an expression of a systemic response purely associated with the catheter handling (67).

A high PVI-related CRP increase during week 1 post-ablation predicts early recurrence of AF during this same first week but not during the entire first month (37,72,97). Moreover, increased CRP concentration 1 month post-ablation is also significantly associated with greater odds of AF recurrence 49 days after PVI (101). Thus, the ablation-induced systemic inflammatory response is associated with early recurrence. Indeed, the body temperature (days 0 to 3 post-ablation) is higher in patients with early recurrence days 0 to 3 post-ablation than in patients without (27,37). Also, anti-inflammatory steroid treatment during the first week following ablation lowers the rate of early recurrence compared with placebo administration (102–104).

Inflammatory cells secrete matrix metalloproteinases (MMPs), which degrade cell and extracellular matrix material in necrotic myocardium

TABLE 2 Predictors of Early Recurrence and Their Possible Mechanisms

Proarrhythmic Mechanism	Predictor of Early Recurrence	First Author (Ref. #)	Observations
Mechanical destabilization	Troponin plasma level	Lim et al. (37)	↑Troponin increase immediately post-ablation predicts early recurrence at days 0–3.
Oxidative stress	Oxidative stress markers in plasma	Richter et al. (72)	↑Myeloperoxidase increase at 6 h to 2 days post-ablation predicts early recurrence at week 1.
Inflammation	CRP plasma level	Lim et al. (37) Richter et al. (72) Lellouche et al. (97)	↑CRP increase at week 1 post-ablation predicts early recurrence at week 1.
	Maximum body temperature	Koyama et al. (27) Lim et al. (37)	↑Body temperature at day 0–3 post-ablation in patients with early recurrence at days 0–3.
Autonomic nervous disbalance	S100B plasma level	Scherschel et al. (140)	↓S100B increase immediately post-ablation occurs in patients with early recurrence at months 0–3.
Less scar formation	TGF-β plasma level	Sasaki et al. (152)	↓TGF-beta increase at 3 months post-ablation occurs in patients with recurrence at months 2–12.
	MRI late gadolinium enhancement	Peters et al. (163)	↓Ablation scar in right inferior PV at 46 days post-ablation in patients with recurrence at months 1–6.
Stretch	ANP plasma level	Okumura et al. (188)	↑ANP 2 months post-ablation in patients with recurrence at months 2–14.

ANP = atrial natriuretic peptide; CRP = C-reactive protein; MRI = magnetic resonance imaging; PV = pulmonary vein; TGF = transforming growth factor.

(105,106). The plasma MMP-9 concentration raises immediately after ablation in AF patients and stays elevated in the long term, although the association with early recurrence is not established (107,108). In murine studies, the inflammatory factor tumor necrosis factor (TNF)-α causes a high MMP concentration (109), atrial fibrosis (110), and proarrhythmic alterations in calcium handling (110–112). There is no agreement on whether elevation of TNF-α plasma concentration occurs after AF ablation in patients (113,114).

Systemic or atrial inflammation due to AF is often already present prior to ablation (115), although a period of sinus rhythm may decrease the inflammatory state in AF patients (116–118). Thus, AF patients without early recurrence during the blinding period may be subjects to an attenuation of the preexisting atrial inflammation, which could reinforce the antiarrhythmic effect of ablation. Conversely, early recurrence sustains the inflammatory atrial substrate in a positive feedback loop (AF begets inflammation that begets AF). It is probable that this contributes to the association between early and late recurrence. Indeed, inflammatory suppression by oral colchicine intake during the entire blinding period following atrial ablation results in both less early and late AF recurrence than does placebo administration (119).

Taken together, ablative PVI causes a time-dependent local and systemic inflammatory response that promotes a proarrhythmic state in atria caused by slowing conduction, altered calcium handling, and structural abnormalities facilitating reentry and triggered activity. Acute ablation-induced inflammation during the first post-ablation days predicts early recurrence in these early days, after which no association between inflammation and recurrence is evident. Anti-inflammatory treatment is effective against early AF recurrence.

Autonomic nervous activity. PVI can injure the myocardial autonomic nerve fibers and ganglionated plexuses (GPs) because the latter are located in close relation to the PV-LA junctions (6). A disbalance of autonomic nervous activity has been suggested to underlie early recurrence after ablation (86,96,120), as parasympathetic or sympathetic activity promotes AF (121,122). Indeed, an autonomic nervous disbalance between the sympathetic and parasympathetic branches pre-exists in AF patients because heart rate variability (HRV) parameters are increased in these patients compared with healthy control subjects (123). Parasympathetic stimulation shortens the action potential in human atrial myocytes via acetylcholine-dependent potassium current (124) and causes heterogeneous shortening of atrial refractoriness in dogs (125). Sympathetic stimulation increases L-type calcium current and intracellular calcium content leading to delayed afterdepolarizations (126,127). The combination of pharmacological parasympathetic and sympathetic stimulation facilitates AF induction and increase AF duration compared with sole parasympathetic stimulation in dogs (128).

As a consequence, direct GP ablation has been thought to have a favorable effect on ablation success via permanent parasympathetic denervation, and several randomized trials evaluating the additional effect of GP ablation to PVI have been conducted (129–132). Although the catheter-based studies show small additional antiarrhythmic effects (129–131), major complications occurred in a thoracoscopic

surgical study (132). There is consensus that the additional antiarrhythmic effect of GP ablation over PVI alone is not well established (6).

Nerve sprouting. Following neural damage, nerve sprouting may occur and cause autonomic nervous disbalance in the ablation aftermath. GP ablation paradoxically causes an increase of sympathetic and parasympathetic nerve density in both LA and right atrium in dogs 2 months after the procedure (133). Indeed, the reinnervation is marked by an increase in growth-associated protein 43 in right atrial ablation lesions in dogs 2 h and 1 month post-ablation (134). Nerve injury also causes an elevation of plasma nerve growth factor (NGF) immediately (135) and at days 0 to 3 (136) after ablation in AF patients. NGF promotes predominantly sympathetic nerve growth (137,138), thereby contributing to a proarrhythmic autonomic nervous disbalance after ablation. Indeed, patients with late AF recurrence have a higher increase in NGF day 1 post-ablation than patients without recurrence (5.05 ± 3.75-fold vs 1.77 ± 0.64-fold; $p = 0.011$; the post hoc statistical comparison was performed by one of the authors, L.G.) (136). Because NGF participates also in the inflammatory response to tissue injury (139), NGF levels may be a mere indirect marker of inflammation and not only nerve sprouting. However, S100B, a marker of neural injury, is increased in plasma immediately after PVI in AF patients without early recurrence compared with patients with early recurrence (140). This suggests a causal relation between recurrence and nerve injury.

The idea of continuous modification of autonomic nervous activity after ablation is supported by the observation that heart rate increases during week 1 post-ablation and returns to baseline values from week 4 onward (141–144). Also, HRV changes following atrial ablation (129,135,142–148). Overall, the time and frequency domain parameters decrease within week 1 post-ablation (129,141–143) and return to pre-ablation values at 1 month onward (129,141–143,145). The autonomic changes may persist beyond the blinding period (135,146,147) and may be beneficial because late recurrence of AF is associated with absence of a sustained HRV reduction (142,146–148).

Furthermore, AF itself is causative of autonomic nervous remodeling. Rapid atrial pacing causes an increase in the density and dispersion of sympathetic nerves after 6 weeks but not after 1 week (149). Therefore, early recurrence of AF may sustain a proarrhythmic autonomic nervous disbalance in the atria that in return maintains the arrhythmogenic substrate for AF.

In summary, ablation causes autonomic nervous activity changes that are dynamic throughout the blinding period. A decrease in parasympathetic activity is associated with successful ablation. AF patients with high ventricular rate (≥92 beats/min) 3 months post-ablation have less early and late recurrence (18).

Tissue repair and mature scar. The necrotic ablation lesion is transformed into a mature collagenous scar within the time frame of the blinding period (105,106,150). The dynamic process of cardiac scar formation includes 3 phases characterized by necrosis or inflammation (reviewed previously), fibrosis or proliferation, and long-term remodeling or maturation (106) that may exert pro- and antiarrhythmic effects. The latter 2 are discussed subsequently.

Proliferative tissue repair. The cardiac scar consists of collagen secreted into the interstitial space by fibroblast and myofibroblasts (105). Myofibroblasts are observed in 2-week-old LA ablation lesions in pigs (51). Fibroblasts, fibrocytes, and possibly endothelial cells differentiate into myofibroblasts in response to mechanical stimulation, growth factors such as transforming growth factor (TGF)-β, and inflammatory cytokines including TNF-α (105). Concomitant stretch and (subsequent) TGF-β production are pivotal for myofibroblast differentiation (105,151). The passive stretch of the necrotic ablation lesion during diastolic filling and systolic contraction of surrounding myocardium thus exert a mechanical stimulus for myofibroblast differentiation. In the clinical setting, TGF-β plasma concentration peaks at day 2 post-ablation and returns to baseline at day 7 in patients with and without late recurrence (107). An increase in TGF-β level 3 months post-ablation compared with pre-ablation occurs only in patients without recurrence (2 to 12 months) (152).

Fibroblasts and myofibroblasts form gap junctions with cardiomyocytes (153–156). Coupling between nonexcitable cells with a less negative resting membrane potential and cardiomyocytes depolarizes the resting membrane of the myocyte, thereby precipitating slowed conduction, re-entry, and ectopic activity (58). Indeed, myofibroblast-cardiomyocyte coupling slows conduction in a density-dependent manner in rat neonatal ventricular cell cultures (155). Also, interposition of fibroblasts and newly formed collagen between vital cardiomyocytes creates a discontinuous substrate that is subject to re-entry (157,158).

Scar maturation. In the final stage of scar formation after myocardial infarction, most myofibroblasts undergo apoptosis (106), while others persist in the scar (159). Scar maturation and rigidification occur when

collagen fibers crosslink (106). Indeed, collagen fibers are interspersed in canine PVs 2 to 4 weeks after radiofrequency delivery (68) By weeks 6 to 8 post-ablation, mature collagen matrix containing sparse normal cardiomyocytes is developed (68). The collagen becomes denser, and the lesion area is less cellular in 10- to 14-week-old lesions (68).

Similarly, ablation scar, visualized by late gadolinium enhancement cardiac magnetic resonance, is present in AF patients from 1 month after atrial ablation onward and does not change appearance after 3 months (85,160). This suggests that the development of dense scar concurs with the blinding period and that no maturation occurs after the blinding period. Scar maturation thus coincides with the development of an antiarrhythmic effect during the blinding period. Indeed, patients with more scar are less likely to have late recurrence in contrast to patients with milder scar formation (161,162). Similarly, less ablation scar in the inferior part of the right inferior PV is described in patients with recurrence 1 to 6 months post-ablation than in patients without recurrence (163), although this is disputed (164,165). Thus, ablation scar size appears to be related to AF recurrence.

INTERACTION WITH ANTIARRHYTHMIC DRUGS. A complicating factor in the assessment of the role of pathophysiological mechanisms occurring during the blinding period is the common use of AADs during the blinding period and its termination at the end of the blinding period. Administration of AADs within the blinding period is proposed to facilitate sinus rhythm maintenance and prevent early recurrence, and is therefore routinely prescribed (6,166,167). AAD therapy is discontinued 1 (29), 2 (15,24,39), or 3 months (16,29,116,168–171) after ablation, or later (13). The choice of AAD is decided by the clinician and often is the AAD proven to be ineffective prior to ablation (172).

Two randomized trials demonstrate that AADs (Vaughan-Williams class I+II+III) decrease the incidence of early recurrence within the period of administration (173,174), whereas others observe that AADs (not specified) during a 2-month blinding period are ineffective on incidence of early recurrence (175). Moreover, AADs during the blinding period do not improve long-term success rates (174,176).

The lack of beneficial effects of AADs (class I and III) may be partially explained by their proarrhythmic actions (177–179). Discontinuation of AADs therefore may initiate an antiarrhythmic effect following the blinding period and be the reason for delayed cure after ablation. We propose that clinical trials should take this into consideration when designing ablation studies.

REDUCTION IN STRETCH AS A POTENTIAL ANTIARRHYTHMIC MECHANISM. Necrotic resorption and immature collagenous scar after PVI may alter the mechanics of the atrial myocardium similarly to the observations made in the ventricles after ventricular myocardial infarction (45–48). First, atrial contracture develops in the area of radiofrequency lesion immediately after application (180,181). Later, paradoxical systolic expansion of LA may occur before rigid PV scar develops over the time course of several weeks compatible with the setting of ventricular myocardial infarction (106,182,183). Thus, the mechanical destabilization leading to stretch is limited to the blinding period and is a potential cause of early recurrence because increased atrial stretch causes opening of stretch activated channels and promotes atrial arrhythmogenesis (184–186).

Also, a reduction in stretch is antiarrhythmic. Indeed, relief of mitral valve stenosis by balloon valvotomy in humans shortens atrial activation time and decreases activation time dispersion (187). Stretch attenuation by conversion of a fresh flexible scar into a mature rigid atrial scar may therefore hinder arrhythmogenesis. Indeed, the plasma concentration of atrial natriuretic peptide, a hormone secreted by the atria in response to stretching, decreases 2 months after ablation (188). The post-ablation atrial natriuretic peptide is significantly lower in patients without recurrence (2 to 14 months post-ablation) than in patients with recurrence (188) Congruently, a decrease in PV diameter and in LA volume are associated with successful PVI (189,190). The decrease in dimensions will consequently decrease the PV and atrial wall stress (Laplace law). A reduction of wall stress combined with a possible reduction in mechanical deformation due to rigid scar formation may attenuate stretch-induced arrhythmogenesis. Indeed, the success rate of 93% after Cox Maze surgery in AF patients may reflect extensive scar formation and atrial rigidification induced by the surgical incisions in the atria (191). These patients also experience early recurrences of AF (191).

We speculate that the delayed cure after ablation therapy at least in part arises with the development of permanent antiarrhythmic mechanical changes taking place during the blinding period. A reduction in atrial stretch by ablation scar formation therefore is a potential antiarrhythmic target.

CONCLUSIONS

AF is a complex arrhythmia with multiple possible mechanisms underlying initiation and maintenance. Ablative PVI is successful in 60% of paroxysmal AF patients. AF can recur during the 3-month blinding period after PVI even when the patient may be free of AF in the long term. The implicit assumption that the arrhythmias observed during the blinding period are of a different nature than the predominant AF mechanism that is being targeted (PV triggers) is not substantiated by the literature. The underlying mechanisms of early recurrence during the blinding period is modulated by procedure-induced pathophysiological changes, such as necrosis, ischemia, edema, inflammation, autonomic nervous disbalance, and tissue repair including scar formation. Some of these factors are proarrhythmic and diminish with time leading to a delayed cure, whereas others are antiarrhythmic and wane leading to a delayed therapy failure. The exact relation between the temporal course of early recurrence and ablation-induced processes is not established. It is likely that early recurrence is the result of coinciding proarrhythmic factors in the first weeks following ablation. The development of a permanent antiarrhythmic effect, mediated by attenuation of stretch by ablation scar maturation, is a likely cause of the delayed therapeutic success of PVI. This not only questions the value of complete electrical isolation of the PVs as a preventive therapy for paroxysmal AF, but also potentially guides us to novel therapeutic modalities, for example aimed at reducing local stretch. Finally, the blinding period contains multiple clues for therapy success or failure as well as the predominant AF mechanism. The pathophysiological processes occurring during the blinding period should be included in investigation of the effects of PVI.

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