RISK MANAGEMENT

CardioVascLas-System®

UDI-DI 4260691560009

State of the Art

A review of the international specialized medical, technical and trade literature and comparison of catheter ablation techniques

Updated 2025-03-31

Prepared according to DIN EN ISO 14971:2019/A11:2021 (replacement for DIN EN 1441;1998-01)
MEDICAL PRODUCTS

Trade name	Descriptive name
RytmoLas®	Open-irrigated **E**lectrode **L**aser **M**apping and **A**blation (ELMA) catheter ***RytmoLas®***, and variants

Accessories	Description
Introducers/controllable airlocks, irrigation pump and robotic systems	Manually with long steerable sheaths (AGILIS, St. Jude) Robotic systems (Hanson medical, Mountain View, USA) Magnetic navigation (Stereotaxis St. Louis, MO, USA)

Energy source

Compact Diode laser ***CardioVascLas®*** 30D 1064, ***LasCor®*** GmbH with preset pulses of continuous wave (cw) laser radiation, and with an accessory: a peristaltic pump ***IriFlowLas® LasCor®*** GmbH with integrated foot switch and interface for safety functions.

Development	Manufacturer	Distribution
LasCor® GmbH	***LasCor®*** GmbH	***LasCor®*** GmbH

Applicationfield

1. HD-lasermapping guided ablation of arrhythmogenic myocardium, modulation of retrocardiac ganglion Plexi and of renal and pulmonary artery perivascular innervation.

   For the treatment of drug resistant tachyarrhythmias, hypertrophic arrhythmogenic myocardium (HOCM), and for resistant systemic or pulmonary hypertension.

   All-in-One

2. Variant for side selective interatrial transseptal laser puncture ***ISPunctureLas®***

Table of contents

The *CardioVascLas-System®* consists of

1. The power source, a compact 1064nm diode laser ***CardioVascLas®***
2. The roller pump ***IriFlowLas®,*** an acessory of the laser for catheter irrigation
3. The open-irrigated Electrode-Laser Mapping and Ablation (ELMA) catheter ***RytmoLas®*** for HD-lasermapping guided tissue selective ablation of cardiac arrhythmias, and its variants:
   - ***RytmoLas®m*** for magnetic navigation
   - ***HypertenoLas®*** for treatment of systemic and pulmonary hypertension
   - ***ISPunctureLas®*** for side selective atrial transseptal puncture

The following ***State of the art*** is a review of the international specialized medical, technical, and trade literature concerning catheter ablation techniques.
The ***CardioVascLas-System®*** has UDI-DI identification, Trademarks, and European, USA and Russian Federation patents.

The review is done by focusing on the comparison of our own experience, publications, posters in the worldwide specialized peer reviewed literature concerning all minimally invasive cardio-vascular ablation procedures including DC shock, Radiofrequency current, Cryoballoon, and Laser balloon ablation as well as Pulse Field Ablation.

*For the laser generator **CardioVascLas®** and its accessory, the roller pump **IriFlowLas®** see the operating manuals, and for each of the catheters see IFUs.*

1 High resolution – High Density (HD) - Catheter Mapping Technique

In early 1975 electrophysiological studies were started in pediatric patients with various arrythmias (DFG Project R2 Weber "Endocardial Catheter Mapping") in the Department of Pediatric Cardiology University of Göttingen. By using small sized #2F to #4F catheters with narrow interelectrode distances of ≤2mm for systematic exploration of the heart chambers, endocardial electrical potentials suggesting specific accessory pathway (AP) potentials were registered (Fig 1).

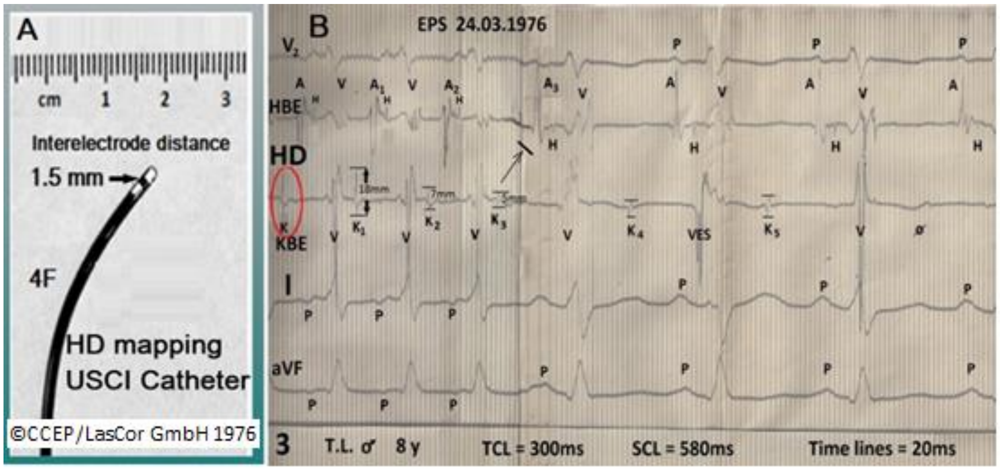


Figure 1
HD = High Density **H** = His-bundle (HBE) and **K** = Kent-bundle (KBE) = *accessory pathway (AP)* electrograms during orthodromic re-entry tachycardia (ORT), with a cycle length (TCL) of 290ms ***showing***: spontaneous gradual dwindling of the accessory pathway potential amplitude from **K** (oval) – **K1** - **K2** -**K3** and eventually block of retrograde atrial conduction over the *AP*: **K3** – **A3** (oblique arrow) followed by sinus rhythm with a sinus cycle length (SCL) of 580ms.

Such AP potentials could by localized by careful catheter exploration from a very limited segment of the atrioventricular valve rings during ORT with retrograde atrial activation but also during sinus rhythm when conduction over the AP with premature ventricular activation (preexcitation) was present (Fig 2).

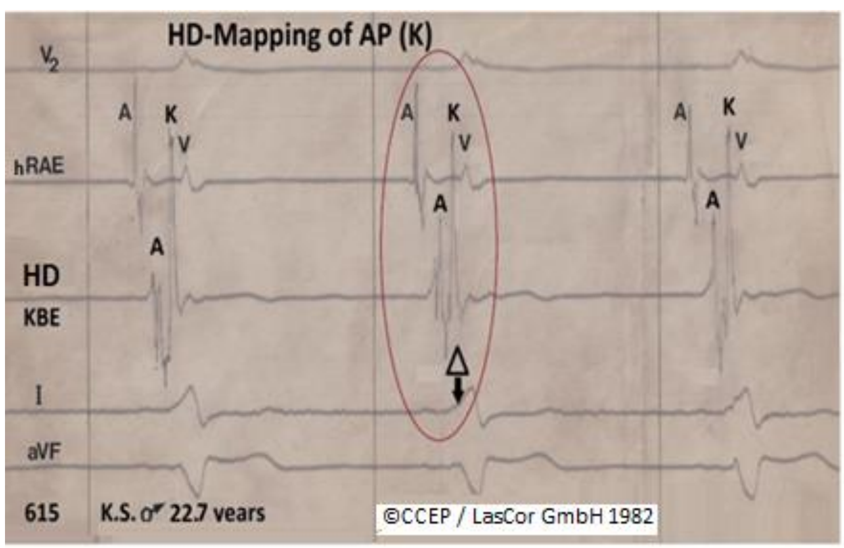


Figure 2
HD KBE = High Density Kent-bundle electrogram (accessory pathway electrogram) recorded from the antero-septal segment of the tricuspid valve ring during sinus rhythm ***showing***: a sharp, high frequency, high amplitude electrical potential **K** (AP potential) simultaneously with the delta wave (vertical arrow) in the surface lead electrogram **I.** **hRAE** = high right atrial electrogram, **V2**, and **aVF** = surface lead electrograms, **A** = atrial and **V** = ventricular potentials.

HD catheter mapping as used routinely since 1975 in our laboratories was recognized as a novel ablation catheter technology that improves mapping resolution and monitoring of lesion maturation first 37 years later(!): ***A PRICE, et al. J Innovations CRM, Research Article, Innovative techniques, 3:599-609, 2012. DOI: 10.19102/icrm.2012.030102.***

Medical treatment of cardiac arrythmias is often not effective and may cause side effects. Success of surgical treatment is also limited and bears the risk of open-heart surgery. Therefore, minimally invasive catheter techniques were developed for the treatment of cardiac arrhythmias, the *catheter ablation technique*. In 1982 the first attempt at closed chest catheter ablation of the atrioventricular conduction system as an alternative treatment of refractory supraventricular tachycardia was reported (N Engl J Med. 306:194-200, 1982). However, this procedure was limited by the subsequent need for permanent pacing in all such patients.

Based on our experience with the localization of specific AP potentials the first successful catheter ablation of a refractory life-threatening cardiac arrhythmia performed in August 1982: ***Catheter technique for closed-chest ablation of an accessory atrioventricular pathway. H Weber, L Schmitz. N Engl J Med 1983; 308:653-54*** *(*Fig 3).

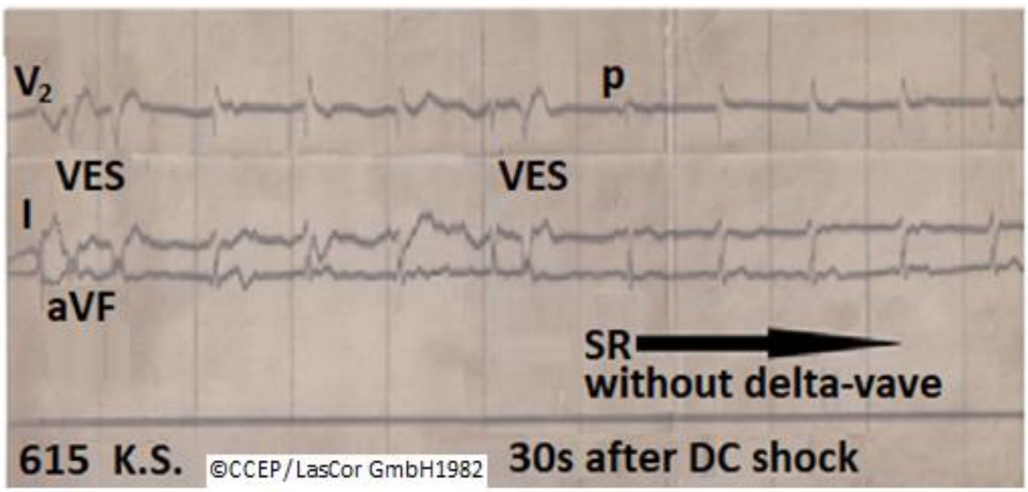


Figure 3
Surface lead ECGs **V2**, I, and aVF after 300J DC shock aimed at the AP potential **K** as shown in the oval in figure 2 ***showing*** the disappearance of the delta wave. VES = ventricular extrasystole, P = p-waves, SR = sinus rhythm.

This was the first successful ablation of an arrhythmogenic substrate in the heart, the cure of a lifethreatening cardiac arrhythmia, a promising alternative to the unsatisfactory drug treatment and the risks of open-heart surgery.

Catheter ablation revolutionized the treatment of cardiac arrhythmias. It is concluded that the importance of catheter ablation for medicine is comparable to that of the discovery of penicillin for the treatment of streptococcal pneumonia:

- **Plumb VJ. *Catheter ablation of accessory pathways of the WPW syndrome and its variants. Progress Cardiovasc Diseases 37:295-306, 1995*.**

Since then, catheter ablation is worldwide the method of choice in the treatment of most tachyarrhythmias. Up to now energy sources used for catheter ablation are radiofrequency (RF) current, Cryoballoon, Laserballoon, Ultrasound, Microwaves, Alcohol injections, and more recently pulse field ablation (PFA).

2 Choice of the ablation energy source

Systematic catheter exploration of the heart chambers during continuous HD catheter mapping by using catheters with ≤2mm interelectrode distances allows for precise localization of arrhythmogenic substrates, of accessory atrioventricular pathways (AP) or of arrhythmogenic foci wherever localized in the heart.

Such specific electrical potentials were found during sinus rhythm or during arrhythmic attacks. Their simultaneous appearance and disappearance with the start and stop of the tachycardia in the HD catheter mapping electrograms, strongly suggested that AP potentials represent the anatomic substrate of the tachyarrhythmia. Additional evidence for this was found by the permanent cure of the arrythmia after DC shock ablation of an AP.

- H Weber, L Schmitz. Catheter technique for ablation of accessory atrioventricular pathway: long-term results. Eur Heart 10:388-399, 1989.

2.1 DC shock

Initially, HD catheter mapping guided DC shock ablation was an intriguing alternative for the cure of arrhythmias. However, DC shock ablation can cause lifethreatening barotrauma. Therefore, other power sources were tested:

- H Weber, L Schmitz, MR Dische, G Rahlf: Percutaneous intracardiac direct–current shocks: Arrhythmogenic potential and pathological changes. Eur Heart J 7:528-537, 1986.

2.2 Radiofrequency RF-current

In our experience in-vivo RF catheter ablation in dog hearts showed unreproducible sizes of lesions with tissue vaporization and crater formation, with the risk of perforation (Fig 4).

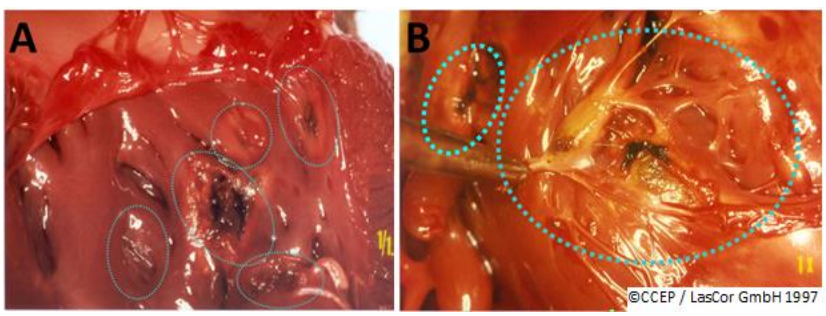


Figure 4
A various sizes of lesions produced by the same level of energy and catheter technique (ovals) ***showing*** also a huge crater with carbonization, and **B** rupture of chordae, hold in a clamp, detached flaps of endomyocardium, crater formation, and mural thrombus (large oval). ***Cardiology 88:346-352, 1997.***

RF catheters with 8-mm-tip equipped with 4 pin-electrodes 1mm in diameters, radially distributed around the tip 0.8 mm from one another, and 3 mm from the distal 8mm ablation tip were presented (Fig 5).

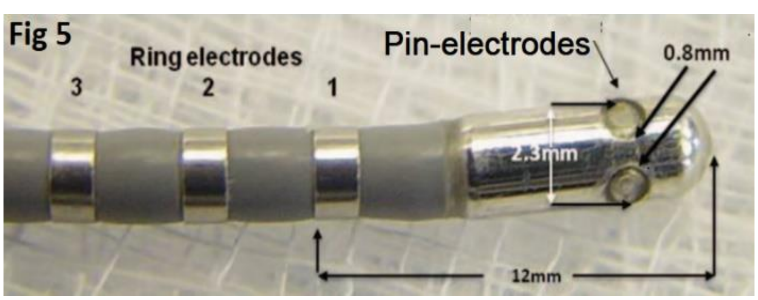


Figure 5
RF catheter with pin electrodes mounted on the distal RF electrode for HD mapping

During RF-ablation profound post ablation changes in voltage occurred in the pin-pin recordings (Fig 6):

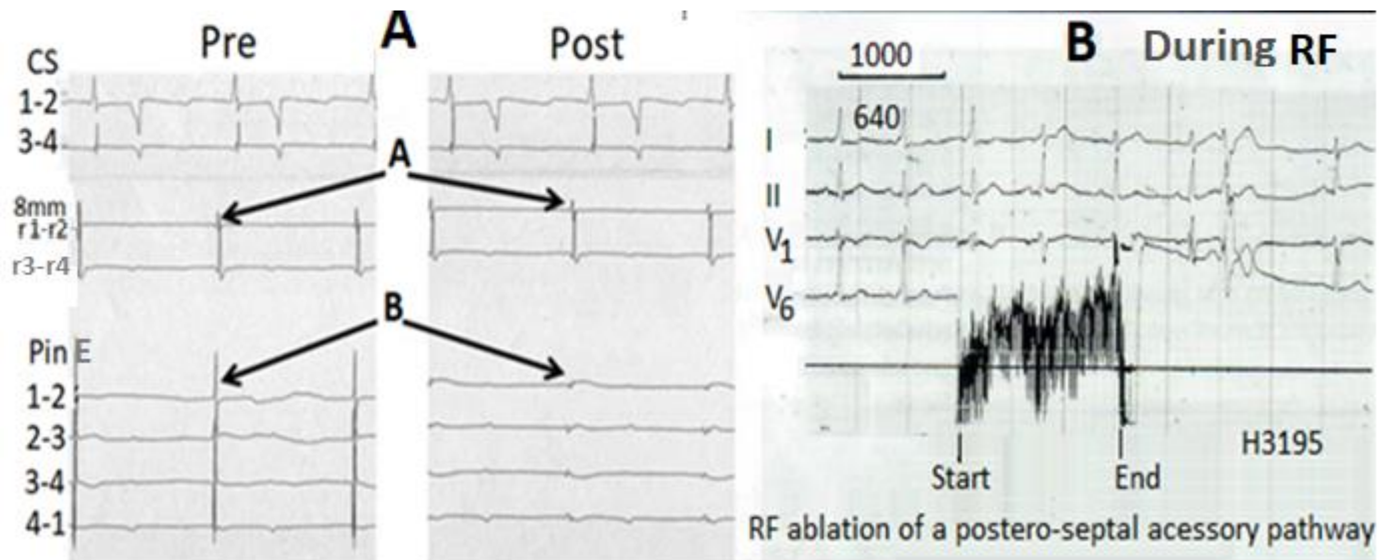


Figure 6 A Changes in voltage pre / post ablation in the tip-ring (oblique arrows A) were minimal whereas in the pin-pin were profound (oblique arrows B), but there were no changes in the coronary sinus (CS 1-2, 3-4).

B However, from the start to the end of RF application electrical hum overlays the electrical potential recorded by the PE.

It was concluded that by using pin electrodes (PE) placed at ≤2mm distances from each other more dramatic changes are shown in electrical potential amplitudes versus the standard 8-mm tip. PE enhances the detection of gaps in the linear lesion. PEs offer significant improvement in the assessment of RF lesion efficacy and provide a useful index of lesion formation and post-ablation lesion mapping and gap detection. Such discrimination is not possible with the 8-mm electrode. "A Novel Ablation Catheter Technology that Improves Mapping Resolution and Monitoring of Lesion Maturation":

- A PRICE et al. J Innovations CRM. Research Article, Innovative techniques, 3:599-609, 2012. DOI: 10.19102/ icrm.2012.030102.

However, during RF ablation PE recordings were superimposed by electrical hum and visual control of RF ablation effects on the monitor are not possible.

To further improve safety and efficacy of RF-ablation novel RF catheters with tip irrigation for cooling, for control of contact force, RF applications with high power/short duration were tested. However, results especially for ablation of persistent atrial fibrillation remained limited.

- ***Sarah Lengauer, Nico Erhard, Miruna A. Popa, Marta Telishevska, Hannah Krafft, Fabian Bahlke, Florian Englert, Felix Bourier, Tilko Reents, Isabel Deisenhofer, Gabriele Hessling "Very High-Power Short-Duration Ablation for Atrial Fibrillation in Adults with Congenital Heart Disease". 24 January 2025. https://doi.org/10.1111/jce.16567*** **Conclusions: "*results for persistent AF were limited*".**

Because of RF risks and limited results, we have used the method only temporarily in animal tests:

- H Weber, A Heinze, S Enders, L Ruprecht, E Unsoeld. Laser vs. Radiofrequency catheter ablation of ventricular myocardium in dogs: A comparative test. Cardiology 88:346-39´52, 1997.

2.3 Cryoballoon

Atrial fibrillation (AF) is a common cardiac arrhythmia that is often managed with catheter ablation, including Cryoablation, to electrically isolate pulmonary veins by tissue freezing. In 2012 a clinical multicenter, randomized trial (gov, identifier NCT01490814) was initiated as a head-to-head comparison of radiofrequency (RF) current and Cryoballoon catheter ablation for the treatment of patients with drug-refractory symptomatic paroxysmal atrial fibrillation. The study evaluated secondary end points that were critical for a representative study interpretation. Consensus documents recognize PVI as a safe and effective strategy for the treatment of AF with either of the 2 leading catheter ablation modalities, Cryoballoon or RFC ablation.

However, despite its effectiveness, a significant complication of Cryoballoon ablation is phrenic nerve injury, which can result in diaphragmatic paralysis (see in: *ÖÇ Karaaslan et al. Late Diaphragmatic Paralysis After Atrial Fibrillation Cryoablation. JAFib and Electrophysiology. Manuscript Number: 20200818*). In addition, on October 10, 2024, Boston Scientific sent all affected customers an Urgent Medical Device Advisory recommending the review of instructions for use related to atrial esophageal fistulas, which include warnings that Cryoablations may cause collateral thermal injury to the esophagus and in rare instances atrio-esophageal fistulas. In the next decade a series of trials may only serve to be a historical reference point as newer or newly redesigned ablation energies and catheters may enter the commercial market space e.g. pulsed field ablation (PFA).

2.4 PFA

Pulsed field ablation (PFA) is an innovative approach in the field of cardiac electrophysiology aimed at treating cardiac arrhythmias. Unlike traditional catheter ablation energies, which use radiofrequency or cryothermal energy to create lesions in the heart, PFA utilizes pulsed electric fields to induce irreversible electroporation, leading to targeted tissue destruction. This pulsed electrical field ablation technology is a revival of an old technology namely, electroporation, that was used in the early days of catheter ablation at different energy settings, largely with high voltages delivered in a single pulse such as the DC shock ablation described above. PFA uses similarly high voltages (i.e., 900–2500 V), but they are delivered in multiple ultrarapid millisecond pulses. The mode of action is considered unique in that this energy ablates nonthermally by creating nanoscale pores in cell membranes. PFA is characterized by tissue-specific thresholds, thereby preferring ablation of myocardial tissue, which has the lowest threshold for PFA. Therefore, in contrast to any other energy source PFA spare collateral structures, such as the esophagus, arteries, lungs, nerves. A state-of-the-art summarizes biophysical principles and clinical applications of PFA, highlighting its potential advantages over conventional ablation methods, outcomes and a reduced risk of thermal collateral damage: ***K.R.J. Chun et al. Europace (2024) 26:1-14, euae134*** https://doi.org/.

However, the above-mentioned characteristics of PFA are not as unique as supposed to be. In a comment by John M. Mandrola: Heart Rhythm Society Meeting 2023 in New Orleans, 2023-06-01 is stated:

" Preliminary data suggest that success rates (of PFA) are not much better than those with traditional ablation. The large EU-PORIA registry series, presented as a late-breaking study at HRS, produced some good and bad news. Good is that the procedure is fast, the learning curve short, success rates are decent. But the bad is the serious complications listed: stroke, tamponade, phrenic nerve dysfunction, air embolism, and coronary spasm", and:

In ***JACC: Asia. 1 Part 2:143–157***, ***2025*** PFA showed non-inferiority to thermal ablation in acute PVI and superiority in first-pass isolation, atrial arrhythmia recurrence, phrenic nerve paralysis or injury, and procedure time. However, PFA treatment exhibited a higher risk of cardiac perforation or tamponade. In contrast: Laser ablation showed superiority to other ablation techniques: ***Letter from the editor in chief in J Innovations in CRM 9:3239-3243, 2018*** and ***Expert commentary of the Mayo Clinic, J Innovations CRM 10:A5, 2019***.

3 PFA vs Laser

3.1 Nonthermal vs. normothermal

1064nm laser application is performed under normothermic conditions: the catheter itself is not heated up – it does not transmit heat – heat is created selectively in myocardium.

3.2 Tissue specificity

The 1064nm laser lesions are produced by <u>tissue selective</u> absorption of photons by myocardium. This ablation effect is based on the low absorption in water and intense scattering of 1064nm laser photons in myocardium (Fig 7).

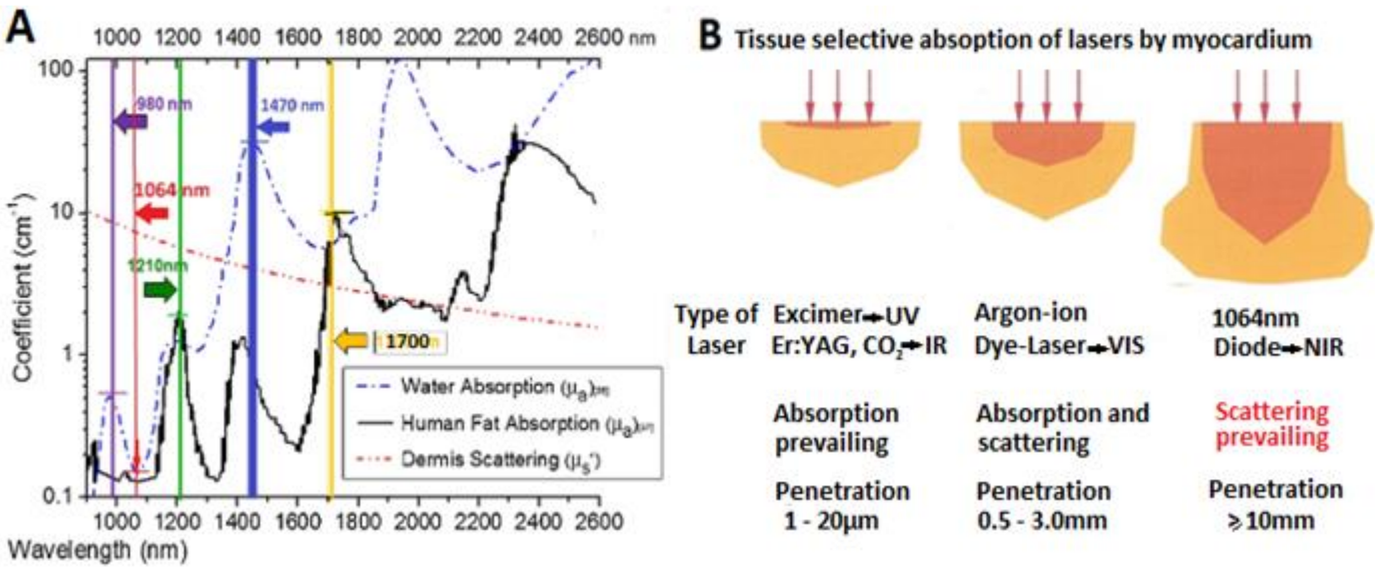


Figure 7 A absorption coefficient of various lasers **B** Selective absorption of the 1064nm by myocardium

- J.L BOULNOIS Quantel, BP 23, 91941 Les Utis-Orsay-Cedex, France. Lasers in Medical Science Vol 1:47-66, 1986

1064nm laser photons are <u>**not absorbed**</u> by transparent tissue such as the endo- and epicardium and <u>**are spared**</u>. Transmural lesions are produced <u>in **seconds,** without tissue vaporisation with crater formation</u> (Fig 8).

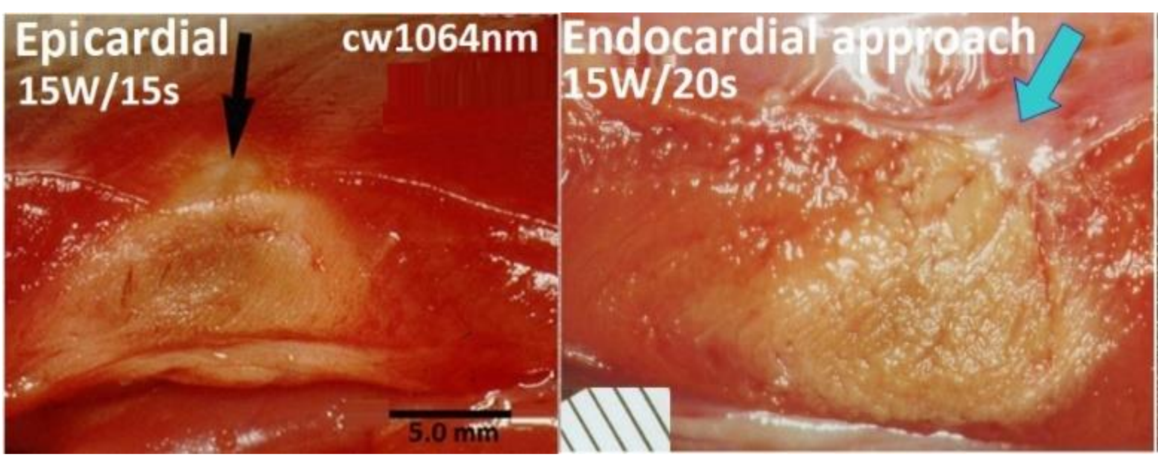


Figure 8

NOTE: The translucient normal endo- and epicardium after LV in-vivo laser application in dog hearts producing homogenous clear-cut transmural lesions. Arrows show catheter orientation during laser application.

3.3 Type of lesion

PFA lesions are often irregular and inhomogeneous (Fig 9).

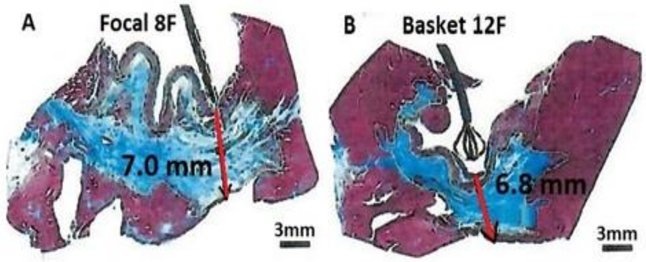


Figure 9
Two **<u>2.5s</u>** bipolar PFA lesions in pig myocardium produced by
A: a linear quadripolar catheter and,
B: by a basket multi-splin 8-pol catheter both showing inhomogeneous irregular lesions.

Histological analysis showed inhomogeneous PFA lesions: a dark central zone with destruction myocytes, edema and hemorrhage surrounded by a pale zone with relatively preserved myocyte architecture with nuclear pyknosis and a hyperstained red outer zone with unaffected normal myocardium. Irreversible lesion depth and diameter are measured by combing the dark central zone and the pale zone. The hyperstained red zone is considered as a reversible area (Fig 10).

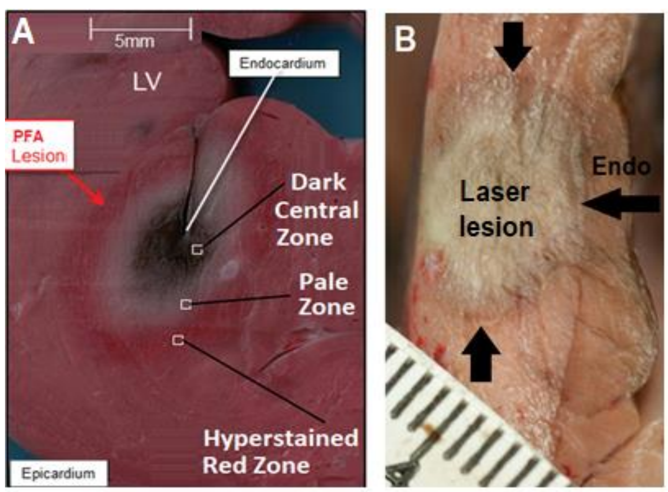


Figure 10
A: Inhomogeneous PFA lesion with three distinct zones: a dark central, pale surrounding, and an outer red zone that is, remarkable, <u>reversible</u>!
B homogenous clear-cut transmural ventricular laser lesion at 15W/15s in a dog heart.

Due to the homogenous distribution of the photon energy in the myocardium, the coagulation process results in a solid volume with <u>well demarcated boundaries</u>. As compared to the PFA lesion the laser has no reversible lesion margins, is not shrinking, in contrast there is a further slight increase in lesion size by heat conduction after the stop of radiation.

3.4 Contact force

Sizes of PFA lesions may vary substantially by applying various catheter contact forces (Fig 11).

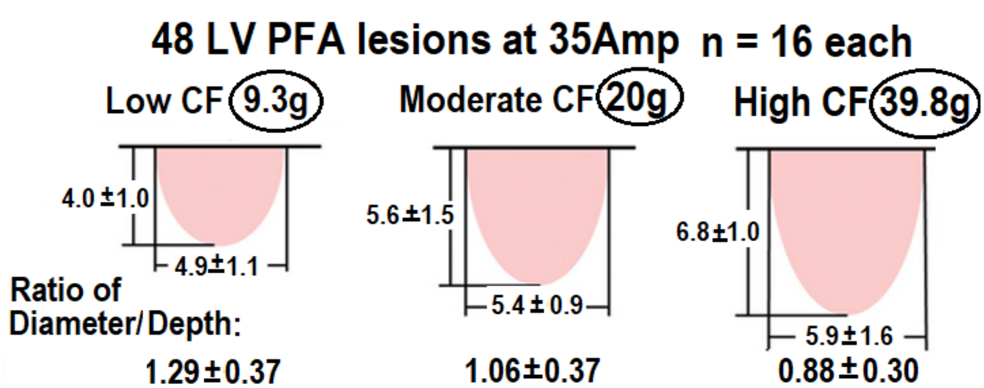


Figure 11 Increase of PFA lesions sizes with the increase of ablation catheter contact force

- H Nakagawa et al. Effects of Contact Force on Lesion Size During Pulsed Field Catheter Ablation: Histochemical Characterization of Ventricular Lesion Boundaries. Circulation: Arrhythmia and Electrophysiology Volume 17, Issue 1, January 2024; Page e012026 https://doi.org/10.1161/CIRCEP.123.012026

In contrast, for 1064nm laser lesion formation there is no need for catheter contact force. Regardless of catheter contact force the same sizes of lesions are achieved (Fig 10):

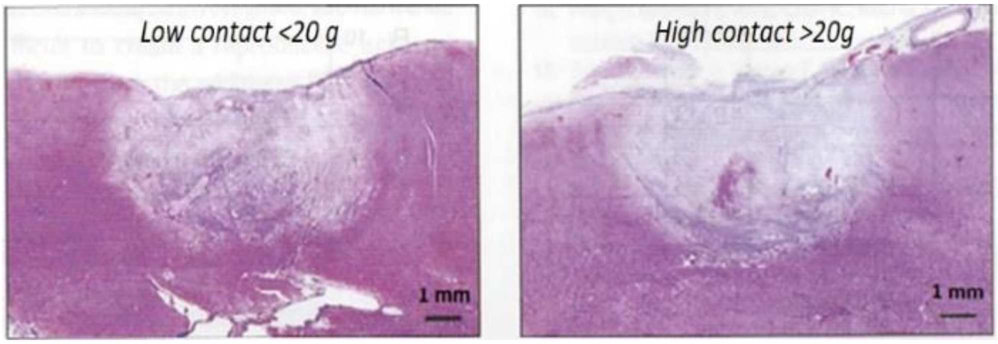


Figure 10
Lesion sizes produced at 20W/cm² for 60s were independent of the applied contact force.
Sizes of laser lesion depend on the level of energy applied, and at a given power depend on the radiation time.

- T Kimura et al. Europace BASIC SCIENCE Vol 17:1309–1315, 2015. doi:10.1093/europace/euu335

- M Sagerer-Gerhardt, H Weber. Open-irrigated laser catheter ablation: influence of catheter-tissue contact force on lesion formation. J Int Card Electrophysiol 42:77-81, 2015

To increase insufficient PFA lesion depth sequential application of RF and PFA was tested. Combined colocalized RF and PFA showed significant increase of lesion size compared with the same dose of PFA or RF alone:

- A Verma, J Maffre, S Farshchi-Heydari. Effect of Sequential, Colocalized Radiofrequency and Pulsed Field Ablation on Cardiac Lesion Size and Histology

3.5 Effect on scarred myocardium

Growth of laser lesion is not hindered by scarred ventricular myocardium. 1064 Laser photons penetrate through fibrous myocardium and are absorbed selectively by the remnant viable myocardium contained in the scar. Lesion formation is not hindered by scarred tissue (Fig 11).

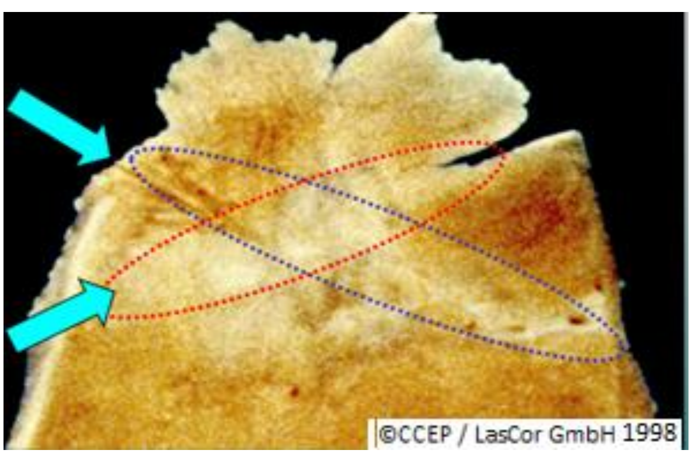


Figure 11
Ventricular Laser scars crossing through each other in a dog heart produced at intervals of 3 months.

Arrows indicate the assumed direction of the laser beam during laser application.

1064nm laser photons are not absorbed by the pale fibrous tissue but are scattered in the scars and are eventually absorbed selectively by the sometimes arrhythmogenic remnant myocardial tissue contained within the scar. This may allow selective laser ablation of arrhythmogenic myocardium contained in post infarction fibrous scar. An important aspect of the laser treatment of postinfarction often lifethreatening ventricular arrhythmias.

- H Weber, A Heinze, S Enders, L Ruprecht, E. Unsoeld. Laer catheter coagulation of normal and scarred ventricular myocardium in dogs. Lasers in Surg Med 22:109-119, 1998.

3.6 Effect on coronaries

During 1064 nm laser ablation coronary arteries are spared. In important safety aspect of the laser method (Fig 12).

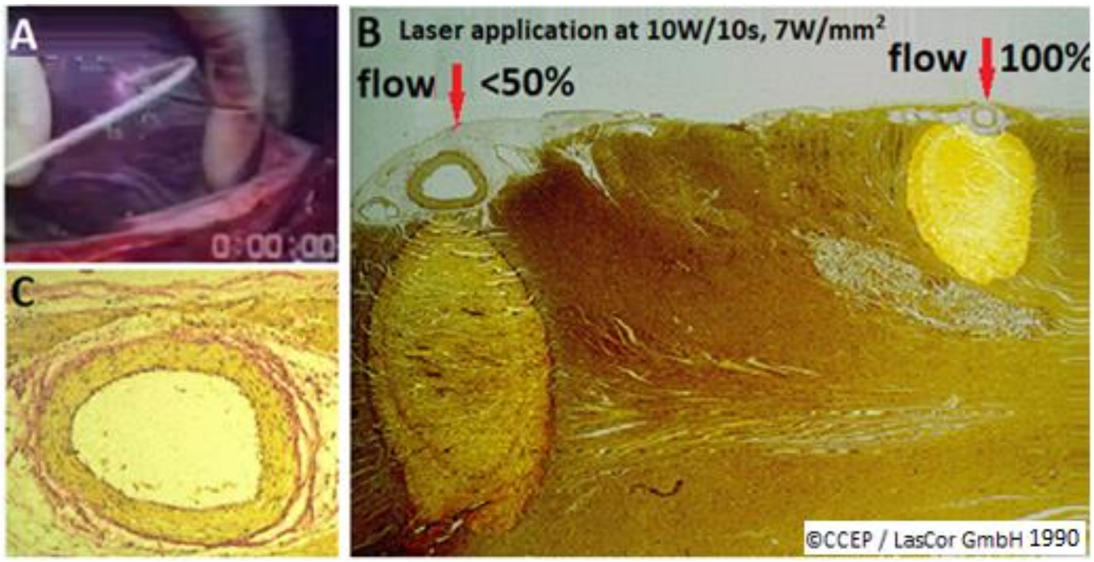


Figure 12

A video image of the laser catheter held hand with its tip upon a pericardial coronary artery during laser application **B** Volumes of 1-2 hours old epimyocardial lesions produced through coronary arteries during normal coronary blood flow were significantly ($P < 0.01$) smaller (31 ± 17 mm^3) than lesions produced through coronaries with reduced (73 ± 22) or interrupted (119 ± 34 mm^3) blood flow (n = 8, each)

C Normal undamaged intima and media of a coronary artery after myocardial laser radiation through the vessel. Free lumen without clot and thrombus formation. A slight inflammatory infiltration of the adventitia is conspicuous around the vessel.

- H Weber, S Enders, K Coppenrath, AB Murray, H Schad, N Mendler. Effects of Nd:YAG laser coagulation of myocardium on coronary vessels. Lasers Surg Med 10:133-139, 1990.

3.7 HD-mapping

3.7.1 During PFA

During very short PFA the electrograms are superimposed by electrical hum. Visual control of electrical potentials on the monitor during lesion formation is not possible (Fig 13).

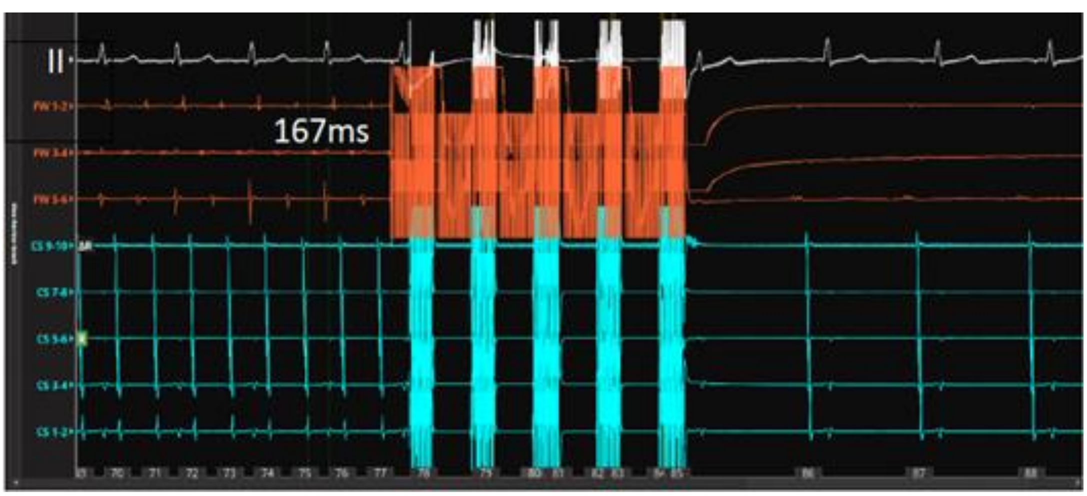


Figure 13

EGM of critical isthmus pre and post 5 PFA applications resulting in microreentrant atria tachycardia termination.

Note: electrical hum is overlapping the ECGs recordings during PFA.

3.7.2 During laser ablation

During laser ablation, lesion growth is visualized on the monitor by the gradual dwindling of electrical potential amplitudes in the HD-lasermapping electrogram because 1064nm laser light does not interfere with electrophysiologic monitoring principles (Fig 14).

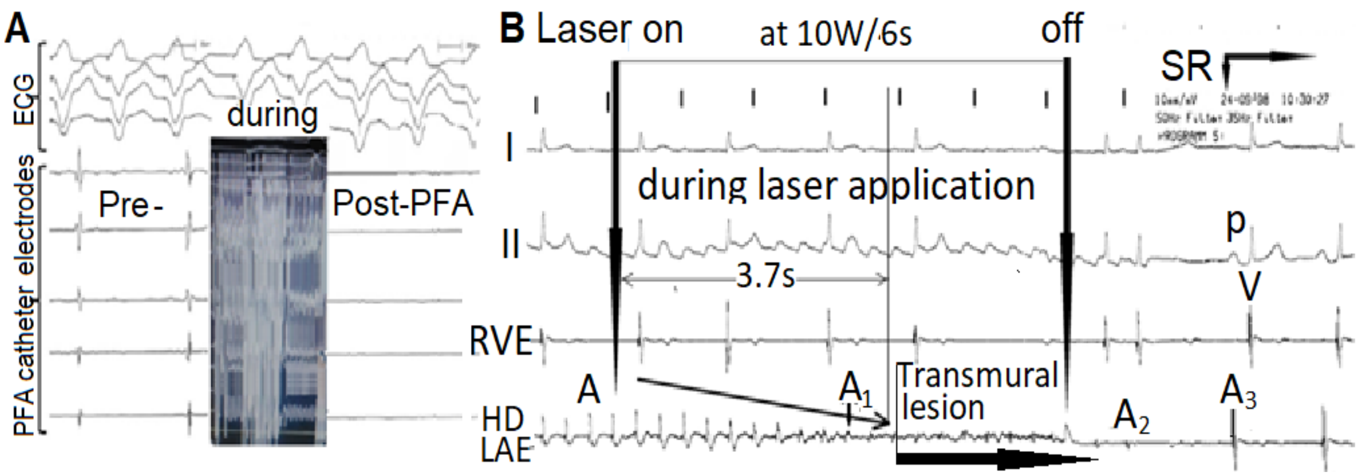


Figure 14 A Endocardial PFA catheter electrogram the ECG overlapping electrical hum during PFA.

B HD-Lasermapping guided AF laser ablation *showing* the gradual abatement and abolishment of potential amplitudes after 3.7s of laser application when transmural lesion can be assumed. The stop of laser after 6s is marked by a slight prong in the High Density Left Atrial Electrogram (HD LAE) pointed by a vertical arrow, eventually followed by sinus rhythm (SR) 2s after timely stop of the laser.

To avoid collateral damages laser application must end with the abolishment of electrical potentials in the Lasermapping recordings.

One of the specific advantages of laser ablation is the ability to perform treatment under normothermic conditions while avoiding interfering with the electrophysiologic principles:

- R Splinter. Laser catheter ablation of cardiac arrhythmias: experimental and basic research and clinical results, in: Lasers in Cardiovascular Interventions. Ed On Topaz. Chapter 16:199-219, 2015.

In contrast to the spontaneous abatement of specific AP shown in the HD catheter mapping, during SVT as shown in Figure 1 during laser application this phenomenon is laser induced and denotes the growth of lesion in the myocardial wall. The important aspect is that with the permanent abolishment of electrical potentials in the HD-lasermapping transmural lesions are achieved. Immediate_stop of laser application currently, currently, the laser lesion remains limited to the myocardial wall saving adjacent tissues such as the esophagus, lungs and vagus nerve.

3.8 HD-Lasermapping

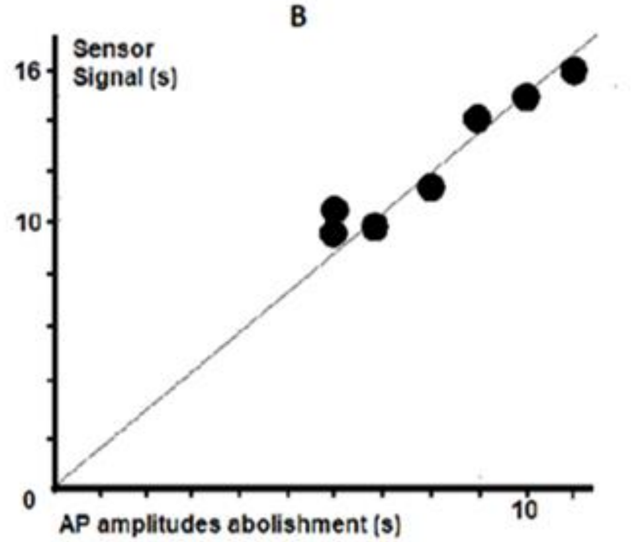
HD-lasermapping allows for immediate real-time verification of the initial success of treatment. This is one of the specific and unique characteristics – a unique advantage - of the laser method that is not practicable with any other ablation technique (Fig 15):

A

LA Lasing Time (s)	Permanent Abolishment of AP Amplitudes (s)	Sensor Signal (s)	Time Difference (s)
5	AP recurrences	Ø	-
10	6	10	+4
10	7	10	+3
10	6	10	+4
20	1	15	+5
20	1	16	+5
30	9	14	+5
30	8	11	+3
	Mean: 8.14 SD: 1.95 p = 0.0058	Mean: 12.3 SD: 2.63	Mean: 4.14

AP: atrial potential; LA: left atrial; SD: standard deviation; Ø: no signal.

Time Differences Between the Permanent Abolishment of Atrial Potential Amplitudes in the HD laser mapping electrogram and the esophageal light sensor alarm signal



Correlation coefficient 0.9 between left atrial HD-laser mapping potential abolishment and sensor signal from the intraluminal esophageal recorded laser light during laser application aimed at the posterior left atrial wall

Figure 15 A Table of time differences between AP abolishment and esophageal temperature sensor signal
B Correlation between AP abolishment and esophageal temperature sensor: 0.9

- H Weber, P Schaur, M Sagerer-G. Use of light sensor and focused atrial electrogram recordings for monitoring thermal injury to the esophagus and lungs during laser catheter ablation of the posterior atrial walls: Preclinical in-vitro porcine and in-vivo canine experimental studies. The Journal of Innovations in CRM 10:3723-3731, 2019.

Timely laser application, stop of radiation with the permanent abolishment of electrical potential amplitudes, in the HD electrogram stops further spread of heat. The lesion will remain limited to the myocardial wall avoiding collateral tissue damage to the esophagus, lungs, and nerves.

When properly applied and executed, the laser lesions will be limited to the myocardial wall saving adjacent anatomical structures such as esophagus and lungs from thermal damage (Fig 16).

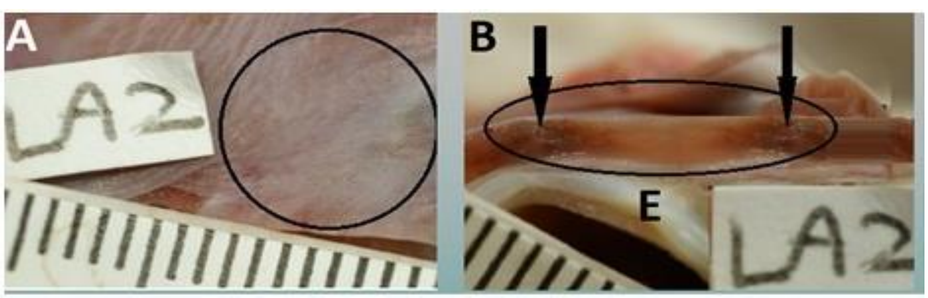


Figure 16 A 5-hour old transmural laser lesion at 10W/10s aimed at the left atrial posterior wall orientated to the esophagus ***showing***: **A** endocardial view (circle) and **B** cross section (oval) a transmural lesion without thermal damage to the Esophageal wall (**E**). LA2 = second laser lesion.

3.9 PFA kidney injury

High voltage PFA pulses can cause hemolysis. Evaluation of the occurrence of hemoglobinuria after PFA and its impact on renal function in patients with atrial fibrillation confirmed acute kidney injury. To prevent PFA kidney injury fluid infusion is needed immediately after the procedure:

- S Mohanty et al. JACC Clin Electrophysiol 2024 Apr;10(4):709-715. Doi: 10.1016/j.jacep.2023.12.008.

3.10 Coronary spasm

Severe ST-segment elevation and coronary spasms during pulsed-field ablation was also reported:

- ***VY Reddy et al. Circulation. 2022 Dec 13;146(24):1808-1819. doi: 10.1161/CIRCULATIONAHA.122.061497. Epub 2022 Sep 22. PMID: 36134574***
- ***D Schaack et al. J Interv Card Electrophysiol 2024 Jun;67(4):675-677. Doi: 10.1007/s10840-024-01813-y. Epub 2024 Apr 23. PMID: 38652213***

Nitroglycerin was suggested to ameliorate coronary artery spasm during focal PFA for AF:

- ***Y Malyshev et al. JACC Clin Electrophysiol. 2024 May;10(5):885-896. Doi: 10.1016/j.jacep.2023.12.015. Epub 2024 Feb 21. PMID: 38385916***

It was assumed that severe vasospasm angina can occur if PFA is performed in proximity to coronary artery, resulting in spasm with ST-segment elevation despite a remote distance from the ablation site to the coronary artery. Therefore, meticulous monitoring of ST-segment changes following PFA delivery even from regions remote to coronary arteries is required.

In contrast, during 1064nm cardiovascular laser application <u>ST segment elevation never occurred</u>. The laser does not compromise coronaries and coronary flow (see also Fig 12).

- ***H Weber, S Enders, K Coppenrath, AB Murray, H Schad, N Mendler. Effects of Nd:YAG laser coagulation of myocardium on coronary vessels. Lasers Surg Med 10:133-139, 1990***

3.11 Laser catheter irrigation

Catheter irrigation is a major prerequisite for safe and effective laser lesion formation. Optimal saline irrigation during laser application was found to be 35mL/min. Saline flow allows for non-contact mode of radiation and creates a clear pathway for the laser light to the target surface.

- ***H Weber, Michaela Sagerer-Gerhardt. Open-irrigated laser catheter ablation produces flow dependent sizes of lesions. PACE 36:1132-37*, 2013**

3.12 Reversible laser effects

Recurrence of electrical potentials amplitudes after stop of radiation prior to the permanent abolishment:

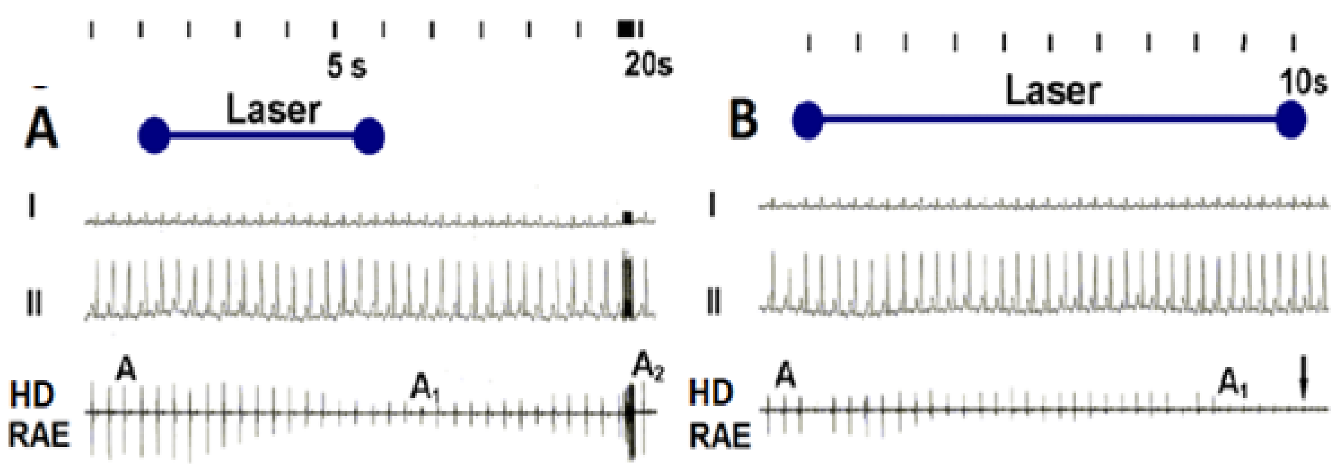


Figure 17 Gradual dwindling of electrical potentials in the high density right atrial electrograms (**HD RAE**) with the start of laser application aimed at the RA free wall (A-A**1**).
A Recurrence of potential amplitudes after 5s (A1-A2), and **B** permanent abolishment after 10s radiation.

Inadvertent laser radiation of the AV node may allow complete recovery of conduction block (Fig 18).

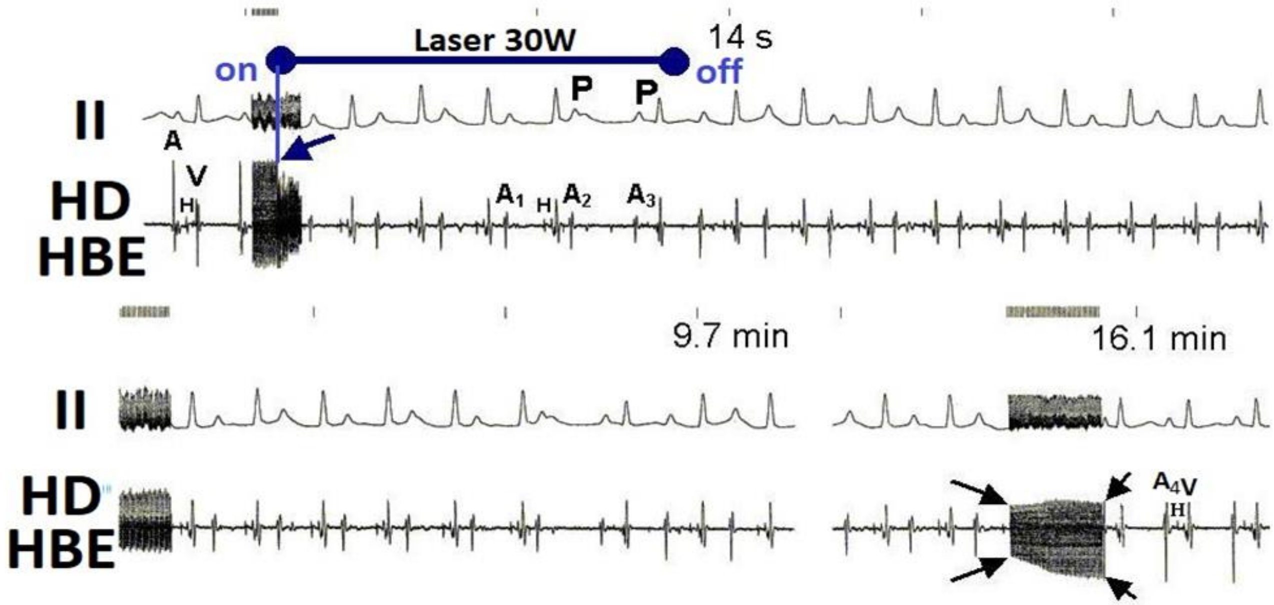


Figure 18 High Density **(HD)** His-Bundle Electrogram (**HBE**) <u>during</u> laser application aimed at the AV-nodal area ***showing*** gradual dwindling of electrical potential amplitudes with the start of laser application (oblique arrow top tracing). Simultaneously gradual lengthening of the proximal (AH) conduction interval is conspicuous (AH to A**1**H). Stop of radiation with the first atrioventricular conduction block (A**2**A**3**, and PP in surface ECG II) gradual increase of electrical potential amplitudes (oblique arrows bottom tracing) and gradual shortening of AVN conduction to normal values is achieved after 16.1 min (AH vs.A**4**H):

- ***H Weber Hot versus cool ablation. J Cardiovasc Electrophysiol 13:440-441, August 2002***

Transient His-Bundle block after interrupted laser application selectively aimed at the His-bundle (Fig 19)

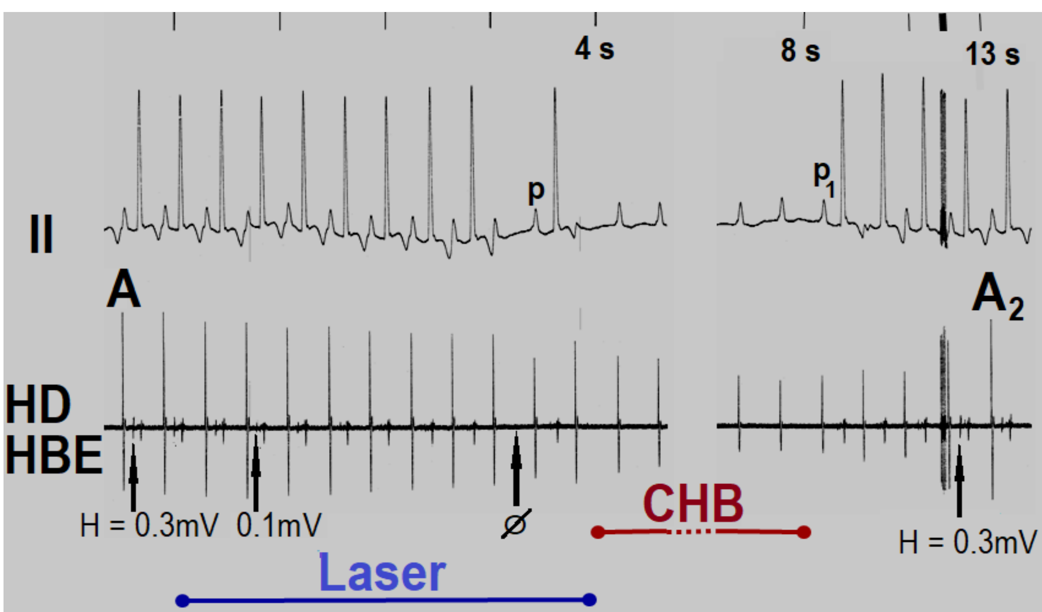


Figure 19 Laser induced (10W/5s) His block (CHB) with complete recovery of conduction and atrial potential after 13s

- H Weber and Michaela Sagerer-Gerhardt. Monitoring laser effects on the conduction system by using an open-irrigated electrode-laser mapping and ablation catheter; laser catheter mapping. Europace 17:664-70, 2015

3.13 Cerebro embolic signals during PFA

Transcranial Doppler (TCD) has been used to monitor the burden of cerebral microembolic signals (CMS) during PFA of atrial fibrillation (Fig 20)

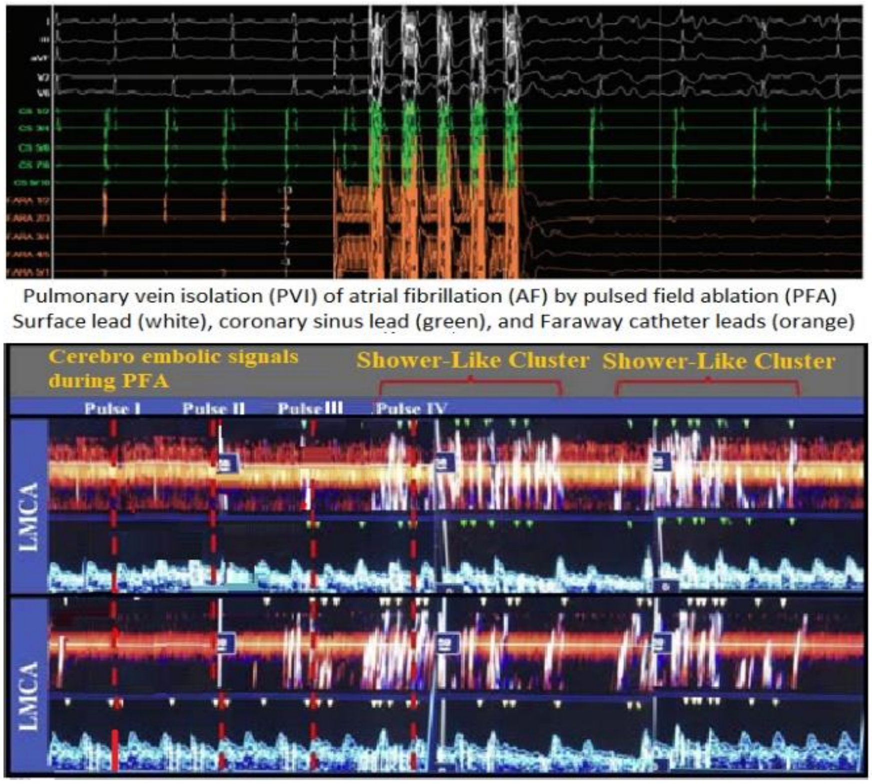


Figure 20
Shower like cluster during PFA

- J Yan et al. Neurol Res. 2021 Nov;43(11):867-873. DOI: 10.1080/01616412.2021.1939488.

Cerebral microembolic signal (CMS) burden generated during PFA by using robotically assisted transcranial doppler and magnetic resonance imaging. CMS are frequently clustered in short lasting shower-like patterns (Fig 21).

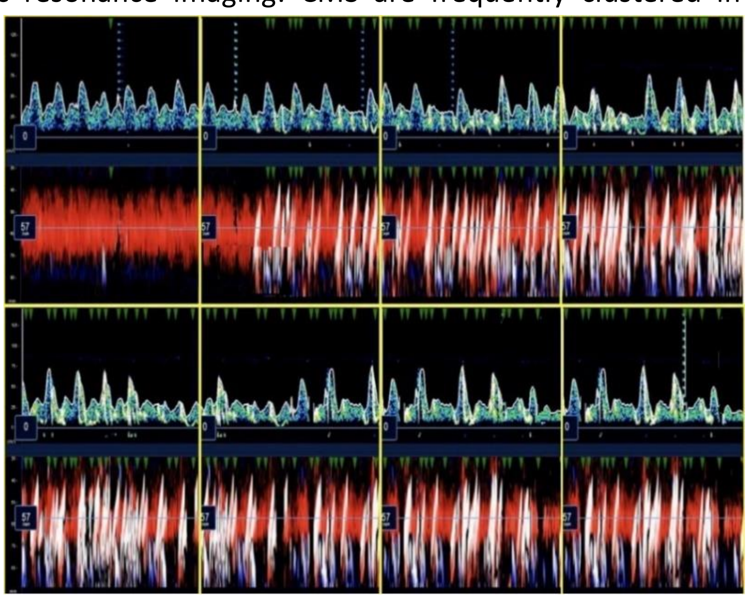


Figure 21
Multiple cerebral microembolic signals (CMS) clustered in a show-like pattern temporarily correlated with PFA. CMS are considered a surrogate marker for stroke risk during AF ablation with PFA.

- D Della Roca et al. Europace 25 Supplement 1, 10.4.5 – Rhythm Control, Catheter ablation

After RF ablation, D-dimer levels increased from a baseline value of 29±28 to 188 ± 138 µg/liter. There was no D-dimer levels correlation with the number of RF lesions produced or the duration of the procedure. RF ablation has a thrombogenic effect that persists through 48 h after the procedure.

A Manolis, Helen Melita Manolis, V Vassilikos, e al. Thrombogenicity of Radiofrequency Lesions: Results with Serial D-Dimer Determinations. J Am Coll Cardiol 1996;28:1257-61.

In contrast, laser ablation is not thrombogenic:

- A Ikeda, H Nakagawa, H. Weber et al. Open-irrigated laser catheter produces deep lesions <u>without thrombus</u> or steam pop. Heart Rhythm Vol 8 No 5, May 2011 pS1-S576 Suppliment PO1-83.

However, as reflected by unchanged plasma D-dimer levels laser ablation is without thrombogenic effect either immediately or at long term after the procedure. (Fig: 22)

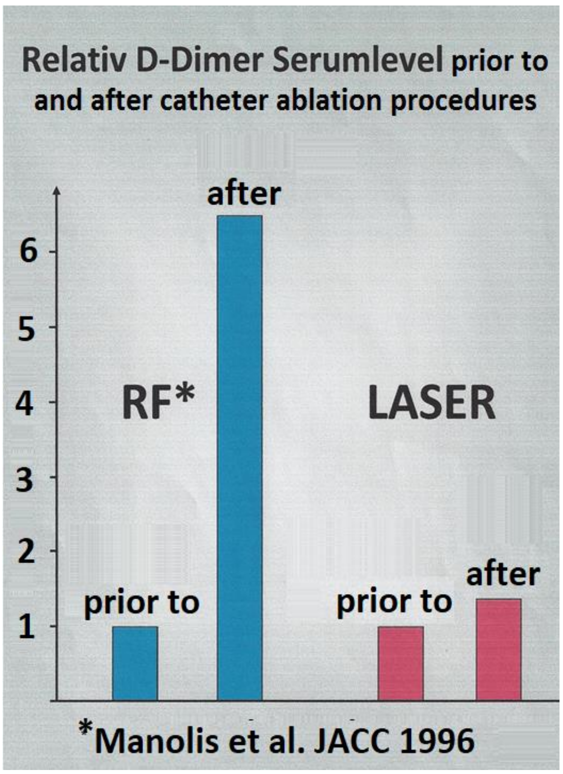


Figure 22
- S Zhuang, H Weber, A. Heinze, et al. D-dimer serum levels after laser catheter ablation of tachyarrhythmias. PACE 22:A94 P196, 1999.

In an experimental study in sheep all laser lesions were visualized as white spots on the endocardial surface without thrombus formation. The in-vivo study showed that laser ablation at 15-20 W for 15-40 s seems to be optimal for achieving the deepest transmural lesions in the atrium and ventricular myocardium without tissue vaporization with crater or thrombus formation.

- HI Condori Leandro, AD Vakhrushev, LE Korobchenko, EG Koshevaya, LB Mitrofanova, NS Goncharova, EM Andreeva, EN Mikhaylov, DS Lebedev. Acute effects of laser myocardial ablation in ex vivo and in vivo experiments. Journal of Arrhythmology. 2021;28(1):47-54.
https://doi.org/10.35336/VA-2021-1-47-54

Note: the laser is the only ablation procedure that is not thrombogenic.
This is a unique characteristic, and an important safety aspect of the laser catheter ablation technique described.

3.14 Outcome of PFA

Posterior wall ablation (PWA) using PFA was achieved in 100% of patients, with a median of 19 (14-26) left atrial PWA. However, recurrent AF/AT was noted in 15% during a median follow-up of 144 (94-279) days (Fig 23).

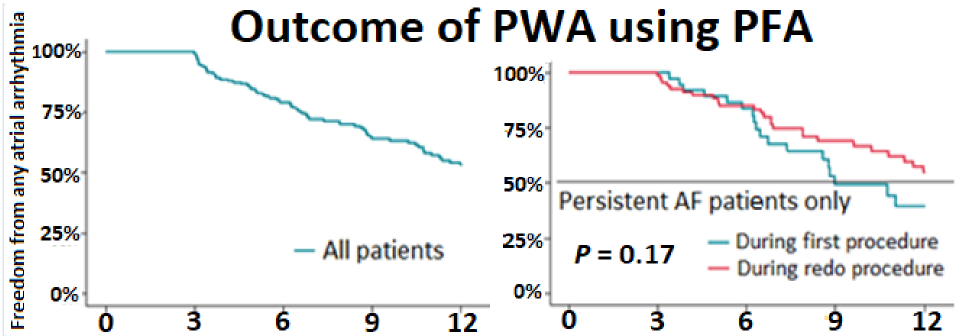


Figure 23 Posterior wall PFA in 215 patients: successful in <u>all patients</u> (100%) by applying a median of **<u>36 (32–44!)</u>** PFA Lesions. Severe adverse events were cardiac tamponade and vascular access complication in one patient each.

Important is that in a median follow-up of 7.3 (5.0–11.8) months the one-year arrhythmia-free outcome was only **53%** and in patients with persistent AF even less (Fig 23 right).

- P Badertscher et al. <u>Left atrial posterior wall isolation</u> using pulsed-field ablation: procedural characteristics, safety, and mid-term outcomes. Journal of Interventional Cardiac Electrophysiology 67:1359–1364, 2024.

In addition, as far as the blanking period is concerned it inflates the true success rate of AF ablation. The success rate of the procedure dropped from 55% to 50% if early recurrences of AF are included. The advent of PFA further exposes the problems with blanking periods because it is increasingly clear that AF recurrences after PFA predict procedural failure. Symptoms after PFA should not be ignored. The primary endpoint should include all episodes from the moment of randomization:

- John M. Mandrola. Are We Inflating the Success Rate of AF Ablation? - Medscape - February 26, 2025.

3.15 Ablation catheters

3.15.1 PFA catheters

Numerous types of PFA catheters with various catheter tip configurations are in test (Fig 24), and the variety of PFA catheters is still widening.

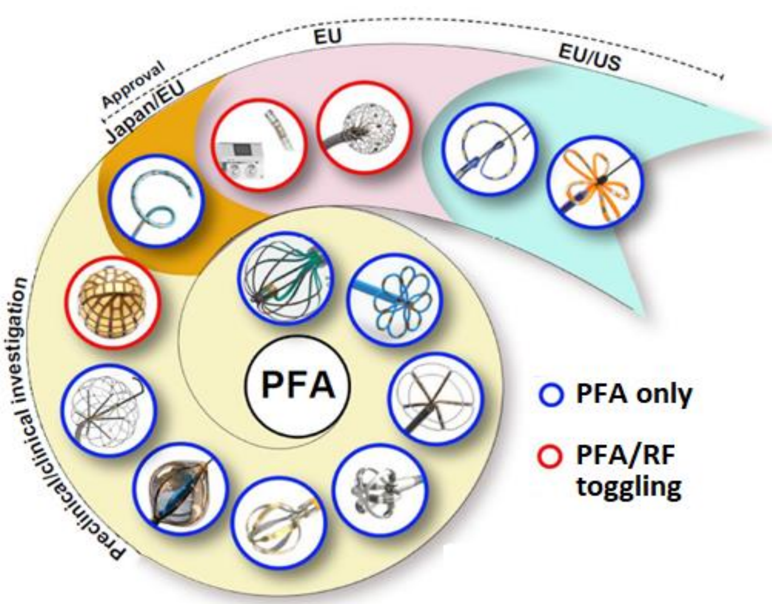


Figure 24
sophisticated PFA catheter tips as used worldwide in the current PFA treatments.

However, to improve PFA combination with <u>RF or cryothermal ablation</u> was used. It is assumed that this may lead to a favourable thermal profile, reduced muscle contractions, and microbubbles while extending lesion.

- A Verma et al. Combined PFA with ultra-low temperature cryoablation: a preclinical experience. J Cardiovasc Electrophysiol 2023;34:2124–2133.

Recently a first clinical trial to include ablation treatment with FARAWAVE TM NAV Pulsed Field Ablation Catheter (Fig 25) in both pulmonary vein isolation (PVI) and posterior wall ablation (PWA) for PersAF in 260 patients was reported.

Figure 25

The primary reason for treatment failure was atrial arrhythmia (AF/AFL/AT) recurrence (defined as ≥30 seconds detected on TTM or Holter or ≥10 seconds on 12-lead ECG) with the majority being AF (28.8%) followed by AFL (10.1%) and AT (6.3%).

Repeat LA ablations were performed in 4.6% (12/260) patients. The PVI durability in re-ablated patients as determined by gap assessment was 84.4% of veins (68.8% of patients). The posterior wall durability was 68.8%.

However, the primary safety event rate was 2.3% including pulmonary edema, coronary spasm, pericarditis. Other safety events included transient phrenic paresis and laboratory confirmed hemolysis and in 50 patients (19.2%) underwent ablation using also a radiofrequency catheter. PFA for PVI 45 applications, and for PWA 32 applications were needed. 4.6% LA re-ablation rate with 84.4% pulmonary vein durability at redo and 68.8% posterior wall durability at redo.

At 12 months, the primary effectiveness rate was 63.5% [57.3% LCL] (Fig 26)

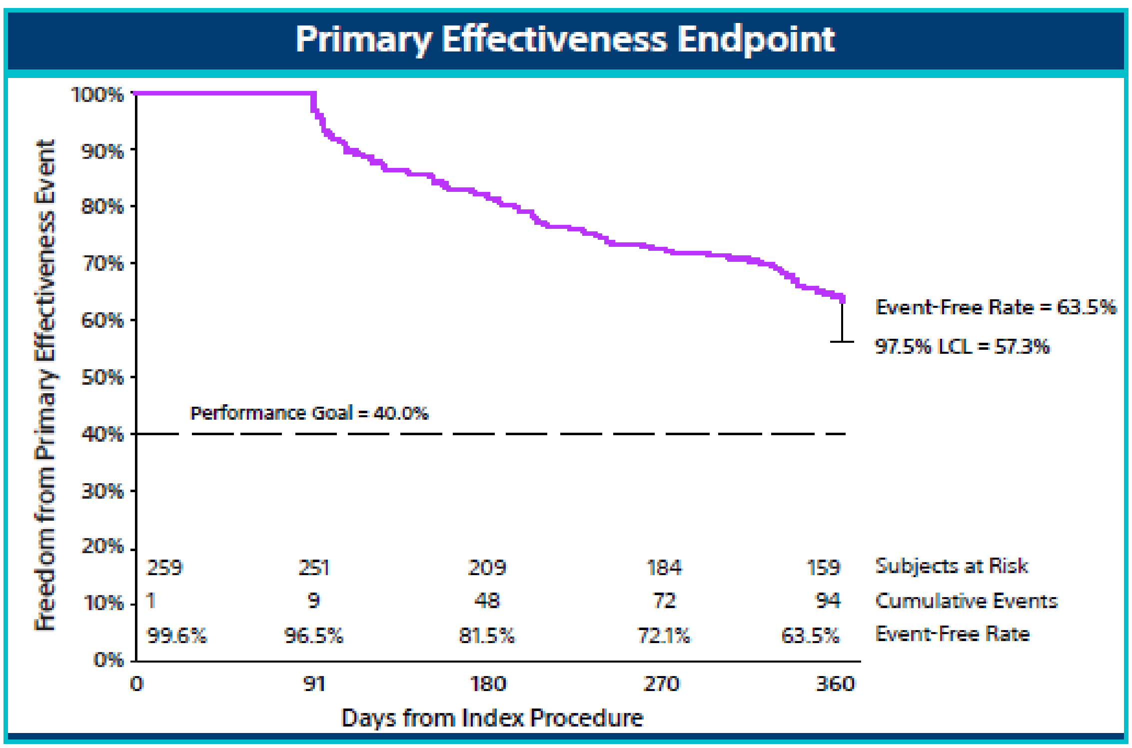
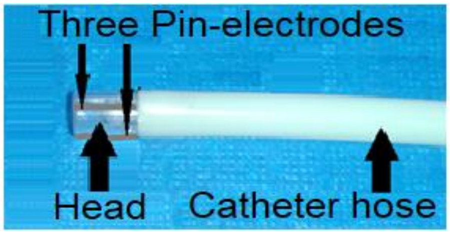


Figure 26

The more sophisticated approach with the FARAWAVE NAV ABLATION CATHETER allows also for magnetic navigation. Additional software shows the operator the ablated areas. This kind of visualization of the lesion shows what we are currently producing anatomically, but the long-term effect on function only becomes visible in the long-term result.

3.15.2 The Laser catheter *RytmoLas®*



The versatile, open-irrigated, electrode laser, mapping and ablation (ELMA) catheter ***RytmoLas®*** has a single configuration. Its transparent tip is provided with three longitudinally orientated cable electrodes at distances of ≤2.0 mm from each other for high density endocardial laser mapping (Fig 25).

Figure 25: the distal end of the ***RytmoLas®***

The ***RytmoLas®*** can be navigated in the cardiovascular system manually, robotically e.g. Hanson Medical but also magnetically (stereotaxis), when provided with magnets at its distal segment (IFU ***RytmoLas®m***). Laser ablation effect is visualized in the HD-lasermapping electrogram showing the result – a transmural lesion! Electrophysiologic monitoring of lesion formation and verification of immediate and real-time laser effect with simultaneous validation of initial success of treatment is very beneficial. Due to the homogenous distribution of photon energy in the myocardium the coagulation process results in a solid volume with well demarcated bounderias. When properly applied and executed, the laser lesion renders negligible risk of arrhythmogenic foci or reentry pathways. Additional software for lesion formation is not needed.

The ***RytmoLas®*** is designed to minimal invasive transluminal catheter directed tretament of various cardiovascular diseases including cardiac arrhythmia, cardio myopathies, systemic and pulmonary resistant hypertention. It is a substrate guided ablation method, with visual assessment of lesion formation. It is an unsophisticated user-friendly system, easy and cost effective to manufacture with elementary components available on the free market.

4 Summary and Conclusions

Laser ablation represents a potentially disruptive technology in the field of cardiology and cardiac electrophysiology, offering a potential paradigm shift in the treatment of cardiovascular diseases. Experimental and clinical evidence supports its efficacy and safety, positioning Laser Ablation as a more than just a viable alternative to traditional ablation methods.

In an editorial comment it was stated that "laser ablation systems should be available in electrophysiology laboratories":

- J. Borbola. Transcatheter laser ablation of atrioventricular nodal reentrant tachycardia — do we really need a newer energy source? European Heart Journal 18, 357-358, 1997

In patients with long lasting persistent atrial fibrillation and comorbidities, the laser rapidly and efficiently (Low power/Short duration) with only a few applications ablates arrhythmogenic atrial areas with a degree of tissue selectivity, a safety profile and a long-term effect heretofore not described for AF ablation.

- H Weber, M Sagerer-G., A Heinze. Laser catheter ablation of long-lasting persistent atrial fibrillation: Long-term results. JAFib 10, Issue 2, 2017

In addition:

1. In *Ex-vivo* Laser Ablation aimed at the posterior wall of the LA with a power of 15 W/<30 s does not lead to visible damage to the esophagus and laser modulation of atrial GP zones is feasible and reduces the inducibility of AF. "No change in atrial effective refractory period is detected following GP zones ablation, when performed from the right atrium":

***- AD Vakhrushev, EI Condori Leandro, IE Korobchenko, LB Mitrofanova, DS Lebedev, EN Mikhailov. Laser catheter ablation of atrial zones with ganglionated plexi: Impact on atrial fibrillation inducibility and the risk of esophageal damage in experimental settings. Journal of Arrhythmology.* 31(2):44-53. 2024. https://doi. org/10.35336/VA-1209**

2. Laser Ablation at 15-20 W / 15-40 s seems to be optimal for achieving the deepest lesions not only in the atrium but also in the ventricular myocardium:

- HIC Leandro, Vakhrushev AD, Korobchenko LE, Koshevaya EG, Mitrofanova LB, Goncharova NS, Andreeva EM, Mikhaylov EN, Lebedev DS. Acute effects of laser myocardial ablation in ex vivo and in vivo experiments. Journal of Arrhythmology. 2021:28(1):47-54.

3. Laser application can achieve selective and permanent renal denervation without long-term collateral damages. The method may become an intriguing alternative for renal sympathetec modulation/denervation in patients with resistant hypertension:

- M Sagerer-Gerhardt, W Haider, K Matiasek, HP Weber. (2021) Catheter Based Renal Sympathetic Denervation by Segmental Endoluminal Laser Radiation in a Pig Model: Anatomical and Histopathological Results. J Vet Sci Ani Husb 9(1): 103

- AD Vakhrushev, HIC Leandro, NS Goncharova, LE Korobchenko, LB Mitrofanova, IA Makarov, EM Andreeva, DS Lebedev, EN Mikhaylov. Laser renal denervation: A Comprehensive evaluation of microstructural renal artery lesions. **Arterial'naya Gipertenziya (Arterial Hypertension) February 2022 DOI: 10.18705/1607-419X-2021-27-6-628-641**

4. In an ovine model percutaneous pulmonary artery laser application was found safe and effective for pulmonary artery denervation procedures. This is a potential treatment for patients with resistant pulmonary hypertension:

- HIC Leandro , E Koshevaya , LB Mitrofanova, AD Vakhrushev, Natalia Goncharova, LE Korobchenko , E Andreeva, DS Lebedev and EN Mikhaylov. An Ovine Model for Percutaneous Pulmonary Artery Laser Denervation: Perivascular Innervation and Ablation Lesion Characteristics. J. Mol. Sci. 2021:22, 8788, pp 1-12.

In contrast:
Unresolved issues of PFA such as optimal energy settings, catheter stability, and the learning curve warrant further investigation. Long-term follow-up data and large-scale randomized controlled trials by using all the sophisticated PFA catheters will be crucial for establishing the role of PFA in the real world:

- K-R J Chun, D Miklavčič, K Vlachos, St Bordignon, D Scherr, P Jais, and Boris Schmidt. State-of-the-art PFA for cardiac arrhythmias: ongoing evolution and future perspective. Europace 26, euae134, 2024

More recently serious periprocedural complications, stroke, occurred in 4 patients after PFA ablation of atrial fibrillation by using VARIPULSE ablation catheters so that

Johnson & Johnson pauses use of FDA-approved PFA system to investigate patient complications

Michael Walter | January 08, 2025 | Cardiovascular Business | Electrophysiology

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Note: With laser ablation we did not encounter any kind of the above mentioned complications.

5 After serious misjudgements about the laser method, it is time to right a wrong:

The ***CardioVascLas®*** laser System is a minimally invasive, painless, non-contact, open-irrigated, low power /short duration, high density (HD) - lasermapping guided ablation procedure with unique characteristics:

1. The 1064nm laser is the only unique tissue selective ablation power source.
   Photons are highly scattered and are selectively absorbed by turbid tissue such as the myocardium. The laser does not produce microemboli or hemolysis causing cerebral or kidney hazards. It does not harm coronaries, in the contrary: coronaries are saved, and, if properly applied initial laser effects such as edema and slight intramural hemorrhage are reversible and permanent conduction blocks are avoided (see PFA!).

2. It is applied under normothermic condition.
   The catheter itself is not heated up, it does not transfer heat and is rather cooled by continuous saline irrigation at room temperature (18°C). Photons are absorbed deep intramurally and are intensly scattered in the myocardial or vessel walls, and are not absorbed by transparent/translucent tissues such as the endo- or epicardium that are spared.

3. Continuous catheter irrigation with heparinized saline at a flow rate of 10mL/min.
   This avoids blood penetration in the open catheter lumen and direct blood contact and burning of the optical fiber which is protected within the catheter with its tip 1.0-1.2 mm from the endhole. The rim of the endhole in intimate contact with the irradiated surface stabilizes the catheter. During laser application increase of the flow rate to 35mL/min is creating a clear pathway for the laser light to the radiation spot.

4. Laser lesions are homogenous, clear-cut, without tissue vaporization with crater formation.
   Starting from deep intramurally transmural lesions are produced at 10-15W, in the atria or ventricles respectively, spreading gradually in the entire myocardial or circumferentially in vessel walls within 10-30s, including in scarred ventricular myocardium thereby inactivating remnant viable often arrhythmogenic myocardium contained in the scar. Laser lesions are not arrhythmogenic. Contact force or catheter orientation are not major determinants for lesion formation.

5. The laser does not interfere with electrophysiologic monitoring principles.
   Growth of lesions is visualized on the monitor in the HD-mapping electrograms by gradual abatement of electrical potential amplitudes during laser applications. Immediate and real-time verification of the success of treatment is very beneficial. Electrophysiologically guided ablation allows for a systematic approach with simultaneous validation of initial success.

6. **HD-lasermapping** guided ablation.
   This is one of the major unique characteristic practicable only by using the laser method as described: when laser radiation is stopped after the permanent abolishment of electrical potential amplitudes, lesions are transmural (Corr. Coeff. 0.9) and are limited to the myocardial wall. Collateral damages to the esophagus, lungs and nerves are avoided.

   For safety resons the CardioVascLas stops automatically after 10s when atrial and after 15s when radiation is aimed atrial or ventricular walls respectively. Preset values in the laser software.

7. Modulation of retrocardiac Ganglion plexi.
   Energy levels as applied for AF ablation aimed at the posterior atrial walls substantially contribute to the long-term success of AF.

8. With the request of *design to cost* (DTC) for competitive products the versatile unsophisticated ***CardioVascLas®*** System is a highly competitive cardiovascular treatment option.

Based on the above mentioned unique characteristics the laser is a superior ablation technique, with the potentials for becoming an all-pervasive procedure for a variety of cardiovascular diseases, including cardiac tachyarrhythmias, resistant systemic and pulmonary hypertension, and cardiomyopathies. In addition, a variant of the catheter provided with magnetic sleeves in its distal segment (IFU ***RytmoLas®m***) was successfully tested for magnetic navigation in the stereotaxis installation, and an optical fiber set designed for a safe side selective interatrial septal puncture procedure (IFU ***ISPunctureLas®***) was successfully tested in studies and was used in patients with the same laser ***CardioVascLas®***:

- ***H Weber, M Sagerer-G. Side-selective atrial transseptal laser punctures. J Innovations CRM 4:1481-85, 2013***

Although as a multicenter trial, the clinical data presented are limited and further studies are warranted. However, preliminary results of the studies, especially the excellent long term results of AF laser ablation in patients with long lasting chronic persistent AF with severe comorbidities are promising. Basis of our data are the in-vitro and in-vivo experimental studies with over 2000 anatomo-pathologically and histopathologically evaluated lesions, furnishing more important insights for rating and assessment of the method.

Laser ablation procedures are fast (low power/short duration), and based on lesion formation under visual HD-lasermapping control are safer. General PFA procedures are rather longer, and milliseconds as compared to a few seconds of laser applications makes no significant difference. PFA impacts are rather too short, and blinded, to allow for immediate evaluation of the effects.

In the future artificial intelligence is expected to contribute substantially to the development and improvement of catheter ablation:

T.M.D**. developed the AI adjudication system. **P.M.** conceived the study design and statistical protocol with input from **I.D., J.-P.A., S.B., A.A., J.J.S., T.D.P., C.D.C., S.G., A.V., and J.D.H. P.M., A.A., D.G**. coordinated the study. **I.D., J.-P.A., S.B., E.G., S.E.M., A.R., J.H., B.B., S.O., S.A., G.T., A.L., Y.G., F.B., J.J.S., T.D.P., C.D.C., S.G., and J.D.H**. performed the study at their respective institutions**. I.D., J.-P.A., P.M., A.A., A.V., and J.D.H**. contributed to the interpretation of the results and to manuscript development**. I.D**. wrote both the first and final drafts of the manuscript. All authors reviewed and revised the final manuscript. **Artificial intelligence for individualized treatment of persistent atrial fibrillation: a randomized controlled trial. Springer Nature, Nature Medicine, Article
https://doi.org/10.1038/s41591-025-03517-w

6 Limitation

This state of the art is by no means exhaustive, nor is it possible in the extremely active world of EP research. It is a summary of a lifetime of research dedicated to the development of minimally invasive procedures to treat and improve the quality of life of patients with cardiovascular disease.

7 Statement

Since 1974 I have performed and conducted numerous experimental and clinical EP studies, by using various catheter techniques and power sources, in research institutes and university laboratories worldwide, and published in over 100 peer reviewed scientific journals and books (see research gate).

Based on these results the laser is not only a non-inferior, but rather a superior alternative for the treatment of catheter directed cardiovascular diseases.

Without the laser, which is undoubtedly a key technology, time and resources will continue to be wasted, and patients unnecessarily put at risk.

8 Note

We have submitted the documents for MDR approval of our products to TÜV SÜD and have received the note for the start of the certification procedure. TÜV SÜD can serve also for FDA approval.

Based on a mutual agreement we are prepared to cooperate with a partner in the approval, production, and marketing of the products.

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Epidemiologist – Specialist Internal Medicine
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Revision history Version A02

Rev-No	Change (revision)	Reason	Date
Rev. 00	Adoption, update and grammar corrections of the original IDE Application CardioVascLas-System® of **TD 04-01 A01 from March 2000-03** into the list of controlled documents for QMH A02 under FB 04-06.2.6_E	MDR-Application TÜV-Süd	2024-07-09
Rev. 01	Updated and supplemented version of the state of the art with comparison of ablation methods	Update	2025-03-31