Assessment of the clinical and electrophysiological characteristics of atrial fibrillation during and after cardiac surgery

Valorization

This thesis highlights the incidence and clinical relevance of late POAF and adds evidence to the notion of opportunities for intensified monitoring of postoperative patients to increase their health and avoid complication related costs.

Late POAF

Atrial fibrillation after cardiac surgery is the most prevalent complication adding to substantial morbidity and clinical costs.[1] Patients developing POAF shorter than 48 hours are discharged without oral anticoagulation and usually without prolonged rhythm monitoring. Although symptomatic late POAF episodes may be diagnosed due to patient's complaints, short subclinical episodes are often left undiagnosed and untreated. Two important clinical questions regarding POAF recurrences are relevant for late POAF, namely the importance of continuous rhythm monitoring and treatment of short lasting AF episodes with oral anticoagulation.

The importance of prolonged continuous rhythm monitoring in AF has recently been emphasized in several reports. Intermittent rhythm monitoring strategies such as Holter monitoring or periodical electrocardiograms is insufficient to uncover the true AF burden.[2, 3] Duration of AF per episode and AF density (i.e temporal clustering of the episodes) are highly unpredictable in all types of AF.[2] This is clearly reflected in clinical misclassification of AF, where only 47% of paroxysmal AF and 32% of persistent AF are correctly categorized.[4] In addition, a large amount of silent strokes result from AF. To quantify the incidence of silent stroke in AF patients, one study conducted cerebral magnetic resonance imaging (MRIc) of AF patients and compared them to sinus rhythm patients.[5] The authors showed that 89% of patients with pAF and 92% of pers AF patients (n= 90 in each group) had underlying silent cerebral ischemia (SCI). Interestingly, 46% of SR group also had SCI. Although significantly less than AF patients, this remains a high percentage of undiagnosed subtle brain damage, which at least partly may correlate to asymptomatic AF. [5, 6, 7] Indeed, asymptomatic AF is usually detected after a stroke episode [8] and using continuous monitoring, asymptomatic AF has been shown to explain a large group of cryptogenic strokes with a median AF detection rate of 41 days after the stroke,[9] further emphasizing the importance of long-term continuous monitoring due to heterogeneous AF density. In line with these findings, we found that the majority of patients without a history of AF also show recurrences of POAF lasting minutes to hours, after discharge from the hospital.

Interestingly, patients with late POAF in addition to early POAF had higher $CHADS_2VAS_2c$ scores. This raises the question of treating short lasting AF episodes, which is still debated. However, accumulating evidence inclines towards anticoagulation treatment for patients with short lasting subclinical AF episodes. First, AF maintains a systemic hypercoagulable state [10] and considering the trias of Virchow, at least in patients with endothelial damage, even short paroxysm of AF may expose the patient to

risk of stroke. In accordance, subclinical AF episodes in diabetic patients doubled the chances of subclinical infarct (up to 60%) and stroke compared to diabetics without AF.[11] Also, recent studies have shown higher hypercoagulability markers, a so called "pro-thrombotic" state, in young paroxysmal AF patients with $CHADS_2VAS_2c$ of 0 compared to patients without AF emphasizing the hypercoagulable state caused by AF.[12] Furthermore, 15 minutes of AF in paroxysmal AF patients significantly increases the levels of platelet activation, thrombin activation and inflammation in the atria compared to patients without AF.[13] In addition, as discussed in chapter 4, subclinical AF episodes detected by continuous rhythm monitoring lasting more than 5-6 minutes are associated with ischemic stroke or systemic embolization.[3, 14] These findings imply that both clinical AF, as well as clinical ischemic stroke, are not sufficient or reliable outcomes for decision making regarding patients long-term treatment. For this reason it is desirable to closely follow patients prone to AF during the months and years after the operation. If AF is detected, intensified monitoring may be adequate and as soon as an AF episode is diagnosed on ECG or Holter anticoagulant therapy should be considered. Furthermore, rhythm follow-up enables to investigate the effects of therapy on individual patients. This is nowadays possible because of the ease and efficiency level of continuous rhythm monitoring devices. Interestingly, detecting AF episodes using an i-phone electrocardiogram application was recently shown to be very feasible and effective and may be the next step in the evolution of effective arrhythmia management.[15] In addition, important outcomes such as silent stroke should also be considered in the decision making process.

Minimal invasive substrate detection in AF

In addition to continuous rhythm monitoring, adequate substrate quantification may contribute to patient selection for further follow up, treatment and perhaps in tailored treatment aimed at underlying substrate. We found that patients developing early and late POAF carry underlying structural substrate as a result of several co-morbidities making minimal invasive techniques to quantify this substrate very attractive. In chapter 4 we used the electrocardiogram to determine P-wave characteristics predicting POAF. Contrary to the direct contact epicardial mapping, the P-wave derived from the ECG gives a reflection of propagation of the entire atrial activation. Lower P-wave amplitude and duration was a characteristic of patients developing early and late POAF. Implementing signal averaged P-wave analysis to detect and predict AF episodes is a low cost low invasive and potentially very accurate technique. Still more research is required to expand the field of ECG based P-wave guided risk stratification in detection and prevention of POAF and AF in general.

In addition, transmural electrical conduction and a 3D substrate is pronounced in remodelled atria and is an important measure of substrate complexity for AF (chapter

5). In chapter 6 we describe a method to simplify endo-epicardial mapping during AF using phase analysis. Phase analysis of electrograms does not require the time-consuming process of activation time annotation and is more and more used to analyse fibrillation electrograms. The coherence of phase between neighboring electrodes allows quantifying the degree of electrical dissociation between these electrodes and thus this technique can also be used for quantifying endo-epicardial electrical dissociation. By calculating the phase of the unipolar electrograms for each electrode, we found that during a measurement of at least 15 seconds, maximum mean phase coherence is highest between closest electrodes on the opposing side (average of 2,3 mm localization error). As expected, we found that there was almost never complete phase coherence between endo-epicardially opposing electrodes, (figure 4 of chapter 6) further emphasizing our findings in chapter 5 where endo-epicardial activation time differences were never completely zero. We also found that phase coherence decays with distance between electrodes. This suggests that dissociated activity is heterogeneously distributed between endo- and epicardium and is not a temporary phenomenon (considering at least the mapped area). If dissociation would be a transient phenomenon, then phase coherence at least with distant electrodes (further than the dissociated region) would reach a plateau and remain constant. This is clearly not the case as seen in figure 3 of chapter 6. Nevertheless, maximum mean phase coherence detects the opposing electrode in longstanding AF patients with endo-epicardial files lasting 15 seconds or longer. In other words, there is a correlation between phase of electrograms and the distance between the electrodes. This technique may contribute to electrode localization on the opposing sites of the atrial wall even in electrically remodeled areas and thus become particularly of interest in quantifying individual substrates for AF for tailored treatment approaches.

In conclusion, for an effective and tailored AF treatment, detection of the severity of the underlying substrate correlating with true AF burden is mandatory. Future research should take primary outcomes such as subclinical short lasting AF episodes and silent strokes into consideration. Modern technology offers solutions for these challenges including enhanced rhythm follow-up with low burden devices independent of patient compliance (ILRs) and minimal-invasive substrate detection and stratification based on low cost low burden diagnostic systems (ECGs).

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