Recent Advances in Subcutaneous Diagnostics and Monitoring

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Abstract - **Current clinical use of implantable cardiac monitors (ICM) includes diagnosing unexplained syncope, unexplained palpitations (symptom-rhythm correlation), arrhythmia monitoring for risk stratification and diagnosing atrial fibrillation (AF) in cryptogenic stroke patients. ICM offer low noise, long term (up to 3 years) and high compliance, continuous monitoring with both automatic and patient activated event storage. Besides arrhythmias, other information such as heart rate variability, mean heart rate during night and patient's daily activity allow for risk assessment in high risk patients: post myocardial infarction (MI) and heart failure (HF).**

Future developments include ST-segment monitoring for early MI detection and monitoring of multiple parameters to allow improved management of HF patients. Additional sensors will be necessary to improve accuracy and to monitor other chronic diseases. Examples include respiratory and body fluid parameters through impedance sensing and hemodynamic parameters using accelerometers or microphones. Long range telemetry and network capabilities enable convenient, automatic data transmission to a secure, clinician website. Clinical studies are designed to demonstrate improved patient outcome and/or lower health care costs.

I. Introduction

Long term monitoring in cardiovascular disease has been hampered by the lack of suitable equipment and lacking patient compliance. Although a wide variety of ambulatory equipment is available that can measure a wide range of physiological parameters, its continuous use over extended periods of time has been limited by discomfort and complexity for the patient. ICMs do not have these disadvantages. Once implanted and correctly programmed, these devices can continuously monitor several important physiological signals, perform real time analysis of the data and detect significant deviations from baseline. Currently ICM devices are available that monitor cardiac arrhythmias, patient physical activity and ECG derived risk stratification parameters.

II. Initial Clinical Experience

The first clinical clinical application for ICMs was for the diagnosis of recurrent unexplained syncope. Several studies have shown that using an ICM yields a diagnosis in more patients compared to conventional testing.

Figure 1 shows a typical example an ECG recorded by an ICM of a patient with unexplained syncope who experiences a recurrence due to atrio-ventricular (AV) block. Based on this ECG finding, a pacemaker was implanted and symptoms were resolved.

Figure 2 shows another example of a patient with infrequent syncopal episodes. Despite multiple short-term ambulatory monitoring the correlation between symptoms and the ECG signal remained unknown. During the first fainting after the ICM implantation a ventricular tachycardia was observed. The patient received ICD therapy.

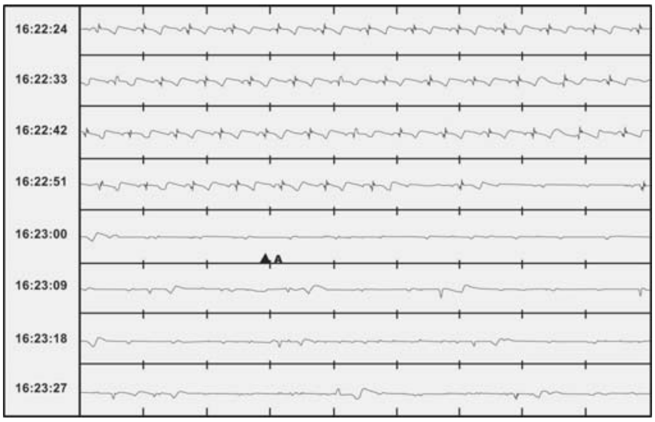

Figure 1. This ECG recording from an ICM was automatically recorded (at the "Δ A"-mark) upon detection of a bradycardia due to AV-block. Since this recording coincided with a recurrence of syncope, a positive diagnosis was made and effective pacemaker therapy was initiated.

Figure 2. This ECG recording from an ICM revealed a sustained ventricular tachycardia causing a recurrence of syncope.

Krahn et al randomized 60 patients with unexplained syncope to either an ICM or to a set of conventional tests, including a 2- to 4-week period of monitoring with an external loop recorder, followed by tilt table testing and electrophysiological testing [1]. Tilt testing was performed with the use of 60° head-up tilt for 30 minutes with continuous ECG and noninvasive blood pressure monitoring. In 14/30 patients randomized to the ICM strategy a diagnosis was obtained versus only 6/30 in the conventional test group. They also reported on the costs associated with syncope diagnosis in this study [2]. The costs per diagnosis was 5852±610 for the ICM and 8414±2527 for the conventional strategy (all costs in Canadian dollars; $p<0.0001$).

After cross-over a diagnosis was obtained in 55% of the patients with an ICM versus 19% with conventional testing ($P=0.0014$). The mean time to recurrence was 117±106 days (median 93 days). Overall, the diagnostic yield in patients randomized to the ICM followed by conventional tests was 50% at a cost per patient of 2937±579 and per diagnosis of 5875±1159. Conventional testing followed by ICM implantation was associated with a diagnostic yield of 47% but at higher costs: 3683±1490 per patient (p=0.013) and 7891±3193 per diagnosis (p=0.002).

Brignole et al reported on 392 patients receiving an ICM for unexplained syncope [3]. At one year, 33% of the patients had a recurrence of syncope, which was documented by the ICM in 26% of cases. Sinus arrest and AV block were the most common arrhythmias during syncope. Based on the recordings from the ICM, a specific therapy was applied in 53 patients: 47 pacemakers, 1 implantable defibrillator, 4 ablations and 1 anti-arrhythmic drug therapy. In these patients, syncope recurrence was significantly lower compared to the patients in whom no specific therapy was applied (0.83 vs 0.07 syncopal episodes per patient per year; p=0.002).

Farwell et al randomized 201 patients with recurrent unexplained syncope to either ICM or conventional testing [4]. After a median follow-up of 17 months, 85 patients had a further syncopal event (48 with ICM and 37 without). 43 patients in the ICM group had a positive ECG diagnosis compared to only 7 in the conventional test group. In all these patients an ECG guided therapy was applied. The use of the ICM resulted in significantly more diagnoses of the cause of syncope being obtained, more rapid application of a ECG based therapy and a greater variety of therapies being applied.

III. Diagnosing Atrial Fibrillation

The assessment of a patient's AF status often is a challenge. First, there is extensive evidence that patient symptoms poorly correlate with AF episodes: many AF episodes are asymptomatic and, on the other hand, many symptoms do not relate to AF episodes. Secondly, intermittent or short term monitoring leads to an underestimation of AF, which may lead to underutilization of anti-coagulation therapy and an overestimation of the effectiveness of rhythm control therapy.

Table 1 shows the various methods for arrhythmia monitoring in general. Continuous, long term monitoring is only provided by implantable devices.

Technology	Storage	Continuous	Electrodes	Comments
Symptoms	None	Yes	None	Only symptomatic events
ECG	< 1 minute	Yes	10 on skin	
Holter	24 – 48 hours	Yes	3 on skin	
Event recorder	7 – 28 days	No	3 on skin	Only symptomatic events
Transtelephonic ECG monitoring	Minutes/ day	No	On skin	Discontinuous
External loop recorder	7 – 28 days	Yes	On wrist or 2-3 on skin	
Mobile cardiac outpatient monitoring	Continuous, (<28 days)	Yes	3 on skin	Direct transmission
Insertable loop recorder	Continuous	Yes	Under skin	Implanted
Pacemaker, ICD	Continuous	Yes	Implanted	Implanted, PM/ICD pt.

Table 1. Overview of currently available arrhythmia monitoring equipment.

In many publications, the high incidence of asymptomatic AF episodes is highlighted. Patten et al reported on a sub-analysis of the SOPAT trial where 1033 patients with symptomatic AF were trans-telephonically monitored for 1 minute per day and during symptoms [5]. They found that 54% of the ECGs that revealed AF were asymptomatic while AF was present in only 37% of the ECGs transmitted upon symptoms.

Nergårdh at al asked patients one week after successful cardioversion about their perceived heart rhythm. Of the 356 patients, 134 were again in AF and only 38 (28%) could indeed tell that they were in AF [6].

Israel et al compared conventional AF monitoring through serial ECG recordings and one 24 hour Holter with continuous monitoring through an implanted pacemaker in a cohort of 254 patients [7]. After one year of follow-up, AF was documented in 54% of the patients through the pacemaker diagnostics and in only 15% of the patients using the conventional methods.

For continuous monitoring in patients that do not require device therapy, an ICM may be considered as an option. These devices are inserted under the skin, normally in the left pectoral region, and feature two electrodes for ECG sensing. AF is detected on the basis of R-R interval irregularity using a two dimensional representation of successive R-R interval differences (figure 3).

Figure 3.Typical 2-dimensional footprints of successive R-R interval differences for sinus rhythm (top panel) and atrial fibrillation (bottom panel).

Clinical applications for diagnosing and monitoring AF include the assessment of ablation success post pulmonary vein isolation and cryptogenic stroke. If AF can be diagnosed in the latter group, these patients can, based on their CHADS-2 score, change their medication from Aspirin® to an oral anticoagulation therapy, thereby significantly reducing their risk on stroke recurrence [8].

IV. Drug Refractory Epilepsy

Zaidi et al performed various cardiovascular tests, including tilt table testing, carotid sinus massage and ICM, to diagnose convulsive syncope in patients with apparent treatment-resistant epilepsy [9]. These patients may have cardiovascular syncope with abnormal movements due to cerebral hypoxia, which may have been mistaken for epilepsy. In 42% of the 74 patients an alternative diagnosis was found. Vasovagal syncope was observed in 20 patients, 2 patients revealed psychogenic symptoms during the head-up tilt test, 7 patients had significant ECG pauses during carotid sinus massage and 2 patients had prolonged bradycardia episodes correlating precisely with seizures according to the ICM. Therefore, cardiovascular evaluation may identify an alternative diagnosis in many patients with apparent epilepsy and should be considered early in the management of patients with convulsive blackouts.

V. Risk Stratification

Risk stratification often includes ECG derived parameters, such as arrhythmias, mean heart rates and heart rate variability (HRV). Little is known about the value of trends in these parameters. Novel ICM also incorporate a number of these risk stratification parameters.

Adamson et al illustrated the potential value of continuous HRV monitoring in HF patients and found in their cohort of 288 patients that HRV was lower in patients at high hospitalization or mortality risk [10]. The sensitivity in predicting cardiovascular hospitalization was 70% with 2.4 false positives per patient-year of follow-up. Combining HRV with other risk stratification parameters, such as mean heart rate at night, patient activity, AF, patient activity, potentially can improve the accuracy of ICMs in prediction hospitalization for worsening of heart failure.

Bloch-Thomson et al implanted an ICM in 297 patients with ejection fraction < 40% within 11±5 days of their acute myocardial infarction and followed these patients for 1.8±0.3 years [11]. Tachy- and brady-arrhythmias were recorded in 46% of the patients, the majority being asymptomatic (85%). New onset AF was the most frequent arrhythmia (32%) while sinus bradycardia, atrio-ventricular block and non-sustained ventricular tachycardia each occurred in approximately 10% of the patients. Atrio-ventricular block lasting at least 8 seconds was an independent predictor of cardiac death (HR 4.8 [2.0-11.5] $p < 0.001$).

A continuous assessment of a patient's risk for a serious cardiovascular event and the ability to alert the patient and/or the physician in an early stage may have a significant impact on health care utilization and costs, quality-of-life and mortality. However, the value of trending of these risk stratification parameters has just become reality and further studies are necessary to identify their true potential and value.

VI. Future Applications

Ongoing research and development in the area of ICM addresses a wide variety of product improvements and new clinical applications.

> Size reduction addresses the issues of ease of implantation – or injection, patient acceptance and sufficient longevity for indications that only require medium-term monitoring.

> The implementation of long range telemetry will allow the device to communicate over arms-length distance, e.g. to a bedside transceiver or mobile telephone that transmits the data further to a secured server on a regular basis, upon symptoms or upon significant events. Once outside the ICM, the collected data can be processed using more complex algorithms running on larger computers. Additionally, long range telemetry enables the device to immediately alert the patient and/or the physician upon an impending event such as worsening heart failure, myocardial infarction or even alert emergency response personnel when sudden cardiac arrest is detected.

> Monitoring strongly depends on sensor technology. The use of electrodes allows both ECG measurements (arrhythmias, HRV, etc.) and impedance measurements. Impedance measurements can provide information about respiration (respiration rate, minute volume), mechanical cardiac function (stroke volume, ejection time) and fluid status (edema). Figure 4 shows an example of an impedance signal derived from an ICM, revealing respiratory and cardiac components. The mean impedance reflects fluid status.

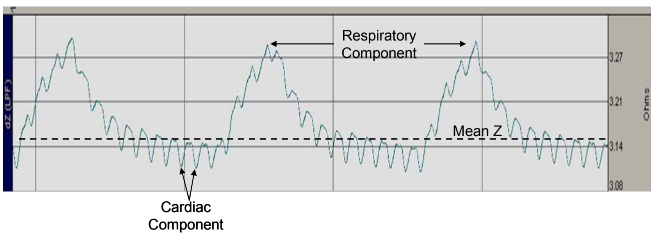

Figure 4. The impedance signal derived from an ICM contains information on many physiological parameters.

> Occlusion of one or more coronary arteries results in an acute MI which alters the mechanical contraction properties of the heart, produces ECG abnormalities such as ST segment and T-wave changes and finally results in chest pain.

ST segment deviations are commonly used for the first diagnosis of MI in patients presenting with chest pain. The ST segment represents an area of the ECG with low frequency content and therefore requires dedicated input amplifiers and filters. Figure 5 shows the subcutaneous ECG recording derived from an ICM during balloon occlusion of the left anterior descending coronary artery. The ST segment deviation from the iso-electric line is clearly visible from this recording and a detection algorithm for these ECG abnormalities can be constructed.

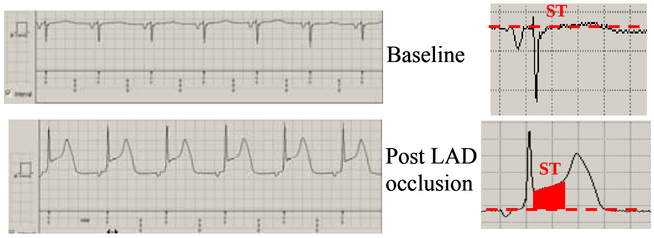

Figure 5. Two subcutaneous ECG recordings derived from an ICM clearly illustrate the ST segment shift following ischemia resulting from the LAD balloon occlusion.

Early detection of MI with immediate call for medical attention is essential to achieve reperfusion before significant myocardial damage occurs. Almost complete myocardial salvage can only be achieved if reperfusion occurs within the first 90 minutes. Minimizing the delay between coronary occlusion and first contact with paramedics mainly depends on the patient's delay until calling for medical attention. An ICM may play an important role in shortening this delay, often resulting from patient denial:

- Chest pain is recognized by the patient and he/she responds immediately
- Alert from the ICM that detects a significant and sustained ST deviation causes the patient to respond
- Chest pain that is initially denied but once confirmed by an alert from the ICM causes the patient to respond

> Mechanical sensors such as piezo-crystal elements or accelerometers can be incorporated in an ICM, enabling the detection of patient activity levels, posture and heart sounds.

> Finally, the bedside transceiver or mobile telephone that is used as a data-hub by the ICM can also be used to indicate by the patient to indicate that he or she is experiencing symptoms and to educate and support the patient in the self-management of his or her disease.

VII. Conclusion

Combinations of the many physiological parameters mentioned above enable the monitoring of a wide variety of cardiovascular diseases. Diagnosing and monitoring is only useful if its results help the physician in guiding therapy or further investigations. Table 2 shows some examples.

Event	Problem	Consequence	Therapy
AF	AF often asymptomatic	Cerebro-vascular accident	Anti-coagulation therapy
AMI	Patient denial	Myocardial necrosis	PCI, stents
CHF	Initially asymptomatic	Decompensation	Diurethica
SCA	Sudden, no defibrillator	Death	Resuscitation, defibrillation

Table 2. Examples of cardiovascular events suitable for diagnosing and/or monitoring through an ICM. Detection of the event will guide therapy. AF=Atrial Fibrillation, AMI=Acute Myocardial Infarction, CHF=Congestive Heart Failure, SCA=Sudden Cardiac Arrest, PCI=Percutaneous Coronary Intervention.

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