Keynote Address
The Last 20 Years in EP: Progress as Viewed through a Focus on the ECG

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The Last 20 Years in EP: Progress As Viewed Through the Focus on the ECG

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United Kingdom
“I am worried in this age of increasing use of sophisticated (and expensive) techniques, about the decreasing ability of our younger colleagues to interpret the electrocardiogram correctly. Invasive procedures with their diagnostic (and financial) rewards have stolen the interest of the younger generation.”

H.J.J. Wellens, 1986
Electrical Stimulation of the Heart in the Study and Treatment of Tachycardias
Wellens Syndrome

ECG abnormality strongly associated with significant left anterior descending coronary artery stenosis. There are 2 types of Wellens syndrome:

- Symmetric deeply inverted T waves in V2 and V3, or
- Biphasic T waves in V2 and V3 (less common), plus
- History of chest pain.
- Normal / minimally elevated cardiac enzymes.
- No pathological precordial Q waves.
- Minimal / no ST elevation.
- No loss of precordial R waves.
The ECG Alphabet

- P
- S
- δ
- R
- Q
- ε
- O/J
- U
- T
- T1/T2
- V
Augustus WALLER (1856-1922)

Cardiograph

Time (sec)

Delay from electrometer to cardiograph was no more than 0.015”

Lippmann Capillary electrometer

1887
Willem Einthoven (1860-1927)

1895

String galvanometer
(Johannes Schweigger)
WPW Syndrome
Louis Wolff, John Parkinson and Paul Dudley White, 1930

The American Heart Journal
Vol. V August, 1930 No. 6

Original Communications

BUNDLE-BRANCH BLOCK WITH SHORT P-R INTERVAL IN HEALTHY YOUNG PEOPLE PRONE TO PAROXYSMAL TACHYCARDIA
WPW Pattern and Syndrome

1st case of Pre-excitation
Cohn and Fraser 1913
PSVT initiated by VPB and
terminated by vagal stimulation

WPW + AVRT

Levine SA, Beeson PB. The Wolff-
Parkinson-White syndrome
with paroxysms of ventricular
tachycardia. Am Heart J

WPW + AF

after Hanon S et al Europace (2005) 7, 28-33
Naming the Delta Wave

[L]a deformation du segment PQ est due a la presence d'une deflexion electrique supplementaire que nous avons propose d'appeler Δ. (Segers, Lequime et Denolin, 1943. 1944). Cette onde qui succede a P presente une amplitude, une duree et une forme tres variables d'un sujet a l'autre.

L'activation ventriculaire precoce de certains coeurs hyperexiteables.

Etude de l'onde Δ de l'electrocardiogramme.

Par M. SEGERS, J. LEQUIME et H. DENOLIN.
Accessory Pathway Theory of Ventricular Pre-excitation


after Hanon S et al Europace (2005) 7, 28-33
Accessory AV Pathway

Epsilon waves are often seen in the ECGs of patients with arrhythmogenic right ventricular dysplasia. These waves are best seen in leads V1 through V4.
Naming the Epsilon Wave

- This letter from Fontaine to J W Hurst is dated March 5, 1997.
- Fontaine discovered and named the epsilon waves. He chose epsilon because it follow delta in the Greek alphabet and it is the mathematical symbol of smallness.

... after discovering the first cases of late (or delayed) potentials recorded at the time of surgery on the epicardium of patients with resistant ventricular tachycardia. It was quite exciting to demonstrate that these late potentials located on the free wall of the right ventricle of patients with arrhythmogenic right ventricular dysplasia could be recorded on the surface by signal averaging and in some circumstances by increasing the magnification of ECG recording.

As late potentials were supposed to be the result of late activation of a limited group of fibers, the term “post-excitation” looked logical, since it was observed after the main excitation of the ventricle,
J Wave

J Point Deviation From Baseline

Differential Diagnosis

- Early repolarisation
- Epicardial or endocardial ischemia or injury
- Pericarditis, hypercalcemia, head injuries, subarachnoid haemorrhage, sympathetic nerve damage in the neck, cardiac arrest from oversedation, Brugada syndrome, Chagas disease
- Right or left bundle branch block
- Right or left ventricular hypertrophy

Kraus - 1920
Bigelow - 1950
Experimental Hypothermia: Respiratory and Blood pH Changes in Relation to Cardiac Function

JOHN J. OSBORN
From the Department of Pediatrics, New York University College of Medicine, New York City

Temporary whole-body hypothermia in theory offers an ideal way of greatly reducing metabolism, and seems to hold great promise in clinical surgery. Yet, although the reptile or the hibernating mammal can withstand very low body temperatures without distress, body temperatures much below 28°C produce severe and often fatal physiological stress in the non-hibernating mammal.

In the course of a series of studies of the physiology of experimental hypothermia in the dog, we have observed profound changes in the auto-regulation of respiration and of blood pH. These changes appear to be important components of the stress effect of low body temperatures in higher mammals. Prevention or control of these changes appears to greatly increase the ability of the dog to survive extremely low body temperatures.

volume was measured directly in several ways, eventually by passage through a recording dry-type gas-meter. The expired air was collected, and in earlier dogs was passed continuously through a modified Marriott bicarbonate buffer solution (a) with indicator dye to provide an estimation of CO₂ concentration. In later experiments, CO₂ concentration of expired air was measured by thermal conductivity in an appropriate pair of cells and gas-train (3). Positive pressure respiration in controllable amount was administered when necessary by means of a Starling pump through a balloon tracheal catheter. Samples of the blood serum were analyzed for CO₂ content and electrolytes by standard clinical laboratory procedures.

Hypothermia Under Moderate Anesthesia. Fremont-Smith (4) has drawn attention to the hyperventilation which coincides with the onset of hypothermia, but it has not been studied intensively. However, large variations in respiratory exchange and in blood pH have recently been related by several investigators to anesthetic shock (3-7). These studies led us to look for similar disturbances during

We have found this current of injury with only one exception in every animal who later fibrillated. It usually begins to show up to 1/2 hour before fibrillation, usually at a rectal temperature under 25° and gradually increases until the usual termination of fibrillation. We have come to look upon it as a very bad prognostic sign”.

Osborn J. Am J Physiol. 1953;175:389-398
A more prominent \( I_{to} \)-mediated spike-and-dome action potential morphology in ventricular epicardium than endocardium, producing a transmural voltage gradient during ventricular activation.
Brugada Syndrome
Lithium-induced Brugada ECG pattern

- 49-y.o. man
- Bipolar disorder treated with lithium, carbamazepine, risperidone
- On admission, serum lithium 2.5 mM/L (therapeutic 0.8-1.2 mM/L)
- No family history of SCD

### Acquired / Unmasked Brugada ECG Syndrome

<table>
<thead>
<tr>
<th>Cardioactive</th>
<th>Class/agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antiarrhythmic drugs</td>
<td>Class IC (flecainide, propafenone, pilsicainide)</td>
</tr>
<tr>
<td></td>
<td>Class IA (ajmaline, procainamide, disopyramide, cibenzoline)</td>
</tr>
<tr>
<td>2. CCBs</td>
<td>Verapamil, diltiazem, nifedipine</td>
</tr>
<tr>
<td>3. Beta-blockers</td>
<td>Propranolol</td>
</tr>
<tr>
<td>4. K+ channel openers</td>
<td>Nicorandil</td>
</tr>
<tr>
<td>5. Nitrates</td>
<td>GTN, ISDN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antihistamines</th>
<th>Class/agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. H1-receptor antagonists</td>
<td>Dimenhydrinate, diphenhydramine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Others substances</th>
<th>Cases described</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cocaine</td>
<td>Overdose or unknown</td>
</tr>
<tr>
<td>2. Alcohol</td>
<td>?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychotropic</th>
<th>Class/agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Tricyclic antidepressants</td>
<td>Amitriptyline, nortriptyline, desipramine, clomipramine, imipramine</td>
</tr>
<tr>
<td>2. Tetracyclic antidepressants</td>
<td>Maprotiline</td>
</tr>
<tr>
<td>3. Antipsychotic</td>
<td>Perphenazine, cyamemazine, trifluoperazine, loxapine</td>
</tr>
<tr>
<td>4. SSRIs</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>5. Lithium</td>
<td>Lithium carbonate</td>
</tr>
<tr>
<td>6. Anticonvulsants</td>
<td>Clonazepam</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Class/agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General anesthetics</td>
<td>Propofol</td>
</tr>
<tr>
<td>2. Local anesthetics</td>
<td>Bupivacaine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other conditions</th>
<th>Cases described</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hyperthermia</td>
<td>H1N1 influenza, pneumonia</td>
</tr>
<tr>
<td>2. Hypokalemia</td>
<td>Liquorice extract</td>
</tr>
</tbody>
</table>
A 48-year-old male, renal transplant recipient was admitted because of pneumonia.

No history of syncope or palpitations and family history negative for sudden death.

Examination: temperature was 39 °C and his heart rate was 120 beats/min.

Cardiac examination was unremarkable.

Early Repolarization
Early Repolarization ECG Pattern

Prevalence

Prevalence, %

General population and controls

Idiopathic VF

Rosso R, et al. JACC 2008;52:1231-8
Early Repolarisation and Long-Term Outcome

- Mobile Clinic Health Survey in Finland
- n = 10,864; 44 ± 8 years; 52% men
- CV disease 8.2%; CAD on ECG 10.2%; LVH on ECG 31.2%
- 1° endpoint: CVM;
- 2° endpoints: ACM, arrhythmic death
- Follow-up: 30 ± 11 years


<table>
<thead>
<tr>
<th>Tikkanen, 2009</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER ≥ 1 mV, total</td>
<td>5.8%</td>
</tr>
<tr>
<td>- in inferior leads</td>
<td>3.5%</td>
</tr>
<tr>
<td>- in lateral leads</td>
<td>2.4%</td>
</tr>
<tr>
<td>- both inferior and lateral</td>
<td>0.1%</td>
</tr>
<tr>
<td>ER &gt; 0.2 mV in inferior leads</td>
<td>0.3%</td>
</tr>
<tr>
<td>ER &gt; 0.2 mV in lateral leads</td>
<td>0.3%</td>
</tr>
<tr>
<td>Reproducibility at 5 years</td>
<td>81.7%</td>
</tr>
</tbody>
</table>

Early Repolarization

Antzelevitch C. Circ J 2012; 76: 1054 – 1065
# Early Repolarisation in Population-Based Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Prevalence, %</th>
<th>Follow-up, years</th>
<th>Risk of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klatsky, 2003</td>
<td>2081</td>
<td>0.9</td>
<td>10-15</td>
<td>HR = 0.8 (0.6 – 1.2)</td>
</tr>
<tr>
<td>Tikkanen, 2009</td>
<td>10,864</td>
<td>5.8</td>
<td>30 ± 11</td>
<td>RR = 2.98 (1.85 – 4.92) for cardiac death&lt;br&gt;RR = 2.92 (1.45 – 5.89) for arrhythmic death&lt;br&gt;RR = 1.54 (1.06 – 2.24) for ACM</td>
</tr>
<tr>
<td>Tikkanen, 2011*</td>
<td>10,814</td>
<td>5.3</td>
<td>30 ± 11</td>
<td>RR = 3.14 (1.56 – 6.3) for arrhythmic death**</td>
</tr>
<tr>
<td>Sinner, 2010</td>
<td>6213</td>
<td>13.1</td>
<td>19</td>
<td>HR = 3.71 (1.44 – 9.53) for cardiac death&lt;br&gt;HR = 4.27 (1.9 – 9.61) for men 35-54 y.o.</td>
</tr>
<tr>
<td>Haruta, 2011</td>
<td>3976</td>
<td>23.9</td>
<td>24 ± 15</td>
<td>HR = 2.5 (1.29 – 4.83) for unexpected death&lt;br&gt;HR = 0.85 (0.78 – 0.93) for ACM</td>
</tr>
<tr>
<td>Olson, 2011</td>
<td>15,141</td>
<td>12.3</td>
<td>17 ± 4</td>
<td>HR = 1.31 (0.94 – 1.82) for SCD&lt;br&gt;HR = 8.77 (3.19 – 24.13) for SCD in white women&lt;br&gt;HR = 0.93 (0.61 – 1.39) for ACM</td>
</tr>
<tr>
<td>Uberoi, 2011</td>
<td>29,281</td>
<td>2.3</td>
<td>9 ± 3</td>
<td>RR = 1.73 (0.93 – 3.3) for cardiac death</td>
</tr>
</tbody>
</table>

* used J point elevation criterion and ST morphology (rapidly ascending or horizontal descending)<br>** for horizontal/descending ST segment; RR = 0.89 (0.52-1.55) for rapidly ascending ST
Early Repolarisation and Long-Term Outcome

- Mobile Clinic Health Survey in Finland
  - n = 10,864; 44 ± 8 years; 52% men
  - CV disease 8.2%; CAD on ECG 10.2%; LVH on ECG 31.2%
  - 1º endpoint: CVM;
  - 2º endpoints: ACM, arrhythmic death
  - Follow-up: 30 ± 11 years

- Survivors of idiopathic VF at 22 centres
  - n = 206; 36 ± 13 years; 59% men
  - All received an ICD
  - n = 412 matched control subjects w/o VF
  - Follow-up: 61 ± 50 years

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<tr>
<th>Haïssaguerre, 2008</th>
<th>Survivors</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER ≥ 1 mV, total</td>
<td>31%</td>
<td>5%</td>
</tr>
<tr>
<td>- in inferior leads</td>
<td>13.6%</td>
<td>-</td>
</tr>
<tr>
<td>- in lateral leads</td>
<td>2.9%</td>
<td>-</td>
</tr>
<tr>
<td>- both inferior and lateral</td>
<td>14.5%</td>
<td>-</td>
</tr>
<tr>
<td>Mean J-point elevation</td>
<td>2.0 ± 0.9 mm</td>
<td>1.2 ± 0.4 mm</td>
</tr>
<tr>
<td>Adjusted OR for the presence of ER</td>
<td>10.9 (95% CI, 6.3 – 18.9)</td>
<td></td>
</tr>
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</table>

Early Repolarization Syndrome

A. Early Repolarization Syndrome in a Healthy Young Male

Surface ECG ($V_5$)

B. Canine Ventricular Action Potentials and ECG

Action Potentials

Control

Pinacidil (2 $\mu$M) $I_{K_{ATP}}$ activator

Endo

Epi

J Wave

ECG

200 ms

50 mV

0.4 mV

C. Pinacidil

Epi 1

Epi 2

ECG

500 ms

D. + 4-AP Ito blocker

300 ms

50 mV

0.5 mV

Antzelevitch and Yan, 2012
Risk Stratification of Patients With ER Pattern: Who Is At Risk?

1. Association of ER pattern with SCD, unexplained syncope, or unexplained family history of SCD.
2. J point or ST-segment elevation $\geq 0.2$ mV in inferior and infero-lateral or global leads.
3. Transient J wave augmentation portends a high risk for VF in patients with ER.
4. Appearance of distinct and prominent J waves.
5. Association of ER pattern with abbreviated QT intervals.
6. Association with horizontal or descending ST segment.
7. Appearance of closely-coupled extrasystole.

ER, early repolarization; SCD, sudden cardiac death; VF, ventricular fibrillation.

Antzelevitch C. Circ J 2012; 76: 1054 – 1065
Idiopathic Ventricular Fibrillation

Role of Purkinje Conducting System Triggers

VPB originating from the R or L ventricular Purkinje system is indicated by a sharp potential (arrow), which precedes activation during sinus rhythm.

RFA abolished VBS and there was no recurrence of VF in 14/16 pts.

The U Wave

Einthoven, ~ 1905; Groedel, 1934

Bradycardia + nor-epinephrine

—, see also Fischer, R.
9998. References prior to 1934 quoted in 4989.
9999. Reference lost.

Modern Electrocardiography - E. Lepeschkin 1951
The Cellular Basis of the U Wave

Antzelevitch, 1994
Long QT Syndrome

CONGENITAL DEAF-MUTISM, FUNCTIONAL HEART DISEASE WITH PROLONGATION OF THE Q-T INTERVAL, AND SUDDEN DEATH

ANTON JERVELL, M.D., AND FRED LANGE-NIELSEN, M.D.
TONSBERG, NORWAY

A COMBINATION of deaf-mutism and a peculiar ear disease has been observed in 4 children in a family of 6. The parents were not related, and were, as the other 2 children, quite healthy and had normal hearing.

The deaf-mute children, who otherwise seemed quite healthy, suffered from “fainting attacks” occurring from the age of 3 to 5 years. By clinical and roentgen examination, which was performed in 3 of the children, no signs of heart disease could be discovered. The electrocardiograms, however, revealed a pronounced prolongation of the Q-T interval in all cases.

Three of the deaf-mute children died suddenly at ages 4, 5 and 9 years respectively.

LQTS Genotype/Phenotype Diagnostic Correlation

LQT1  $I_{Ks}$  KVLQKT1  Exercise
LQT2  $I_{Kr}$  HERG  Acoustic
LQT3  $I_{Na}$  SCN5A  Sleep

Moss A. et al
Myocardial Ionic Currents

Prolongation of APD leads to prolongation of QT interval on ECG

Current

- \( \text{Na}^+ \) Current
- L-type Ca\(^{2+} \) Current
- T-type Ca\(^{2+} \) Current
- Na\(^+\)-Ca\(^{2+} \) exchange
- \( I_{\text{TO1}} \) (4-AP-sensitive)
- \( I_{\text{TO2}} \) (Ca\(^{2+} \)-activated)
- \( I_{\text{KS}} \)
- \( I_{\text{KR}} \)
- \( I_{\text{Kur}} \)
- \( I_{\text{Cl}} \) or \( I_{\text{Kp}} \)
- Inward rectifier, \( I_{\text{K1}} \)
- Pacemaker current, \( I_{\text{f}} \)
Torsade de Pointes
Dessertenne’s Tachycardia
How Should it be Spelled?

• Torsades de pointe
• Torsades de pointes
• Torsades des pointe
• Torsades des pointes
• Torsade de pointe
• Torsade de pointes
• Torsade des pointe
• Torsade des pointes

Each initial letter could begin with an upper or lower case character, thus providing sixty four possible variations
Dessertenne’s Tachycardia

[Ventricular tachycardia with 2 variable opposing foci]
Torsades de pointes - "twisting of the points"

Potassium Therapy for LQT2

Patient #2

$K^+ = 3.7$

$K^+ = 5.9$

Etheridge et al, JACC 2003
Long QT Syndrome
Gene Specific Pharmacotherapy

Flecainide therapy

LQT3

Baseline QTc = 672 msec
Flecainide QTc = 434 msec

Ranolazine and QTc interval in LQT3

LQT3 due to KPQ mutation leading to increased SCN5A – activation of Late Na current

\[ \Delta QTc \text{ vs. [RAN] plasma} \]

\[ r = 0.7 \pm 0.22 \]

\[ \text{slope} = 24.1 \text{ msec/1,000 ng/ml} \]

\[ (P = 0.008) \]

\[ \text{Values are mean} \pm \text{SE from 5 patients} \]

SE from 5 patients

T Wave Alternans - TWA

Ananthasubramaniam and Karthikeyan: Heart 2001; 85:389
T Wave Alternans - Ionic Mechanisms

**Top:** Presence of slowly deactivating repolarising current.

**Bottom:** Residual repolarising current at the beginning of a subsequent AP at rapid heart rate (arrow).

$I_{ks}$, but also mutations of other currents, oscillation of intracellular $Ca^{++}$, etc.

T Wave Alternans - TWA

Armoudas et al, Nature Clinical Practice, 2005
Cambridge Heart TWA Technique
Predictive Value of Indeterminate TWA for Death and SVA in LV Dysfunction

- n = 549, IHD
- Mean EF = 0.25
- Follow-up = 2 years

Bigger TJ, et al. JACC 2006;48:1399-404

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- TWA negative (n=195)
- TWA positive (n=163)
- TWA indeterminate (n=191)

---

Events, %

Bigger TJ, et al. JACC 2006;48:1399-404
N = 566
IHD, EF ≤ 0.40 (mean, 0.28) NSVT
MTWA vs EPS
Follow-up 1.9 yrs
ICD Rx n = 65 (11%)

TWA (non n) vs TWA (-)  \textit{HR} 2.1
EPS (+) vs EPS (-)  \textit{HR} 2.4

\textit{p} = 0.016 both tests negative vs both tests negative

\textit{Constantini et al, JACC 2009 53:471-9}
Heart Rate Variability

Tachograms

<table>
<thead>
<tr>
<th>Normal</th>
<th>Heart Failure</th>
<th>Heart Transplant</th>
</tr>
</thead>
</table>

BPM

Time
HRV and Survival after Acute MI

St. George's Post-Infarction Survey  Prospective Values - EMIAT Data

HRV index > 20  HRV index ≤ 20

1486 pts with LVEF < 40%

p < 0.0001
Heart Rate Turbulence

- Compensatory pause
- Late deceleration phase (TS)
- Early acceleration phase (TO)

RR interval (ms)

Coupling interval

RR interval (ms)
Heart Rate Turbulence Early After MI
CARISMA and REFINE

<table>
<thead>
<tr>
<th>Study</th>
<th>CARISMA</th>
<th>REFINE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>312</td>
<td>322</td>
</tr>
<tr>
<td>Age, years</td>
<td>66 (51-68)</td>
<td>62 (53-70)</td>
</tr>
<tr>
<td>EF, median %</td>
<td>0.31 (0.27-0.36)</td>
<td>0.40 (0.35-0.44)</td>
</tr>
<tr>
<td>BB, %</td>
<td>96</td>
<td>92</td>
</tr>
<tr>
<td>RAASIs %</td>
<td>89</td>
<td>94</td>
</tr>
<tr>
<td>ASA, %</td>
<td>95</td>
<td>99</td>
</tr>
<tr>
<td>Statin, %</td>
<td>82</td>
<td>89</td>
</tr>
<tr>
<td>Arrhythmic events</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>HRT test</td>
<td>5-21 days &amp; 6 weeks</td>
<td>2-4 weeks &amp; 10-14 weeks</td>
</tr>
</tbody>
</table>

The Modern Electrocardiograph

"Declare the past, diagnose the present and foretell the future" - Hippocrates, Aphorisms II
The electrocardiogram is still the cardiologist’s best friend

*Shlomo Stern, Circulation* 2006; 113: 753-56