

IDOSA COM DOR PRECORDIAL OPRESSIVA NO REPOUSO, NÃO IRRADIADA,
MARCAPASSO IMPLANTADO E ALTERAÇÕES DINÂMICAS NA POLARIDADE DA
ONDA T

ANCIANA CON DOLOR TORÁCICO OPRESIVO EN REPOSO, NO IRRADIADO, CON
IMPLANTE DE MARCAPASO Y CAMBIOS DINÁMICOS EN LA POLARIDAD DE LA
ONDA T

ELDERLY WOMAN WITH OPRESSIVE CHEST PAIN CHARACTER AT REST, NOT
RADIATING IMPLANTED PACEMAKER AND DINAMIC CHANGES OF THE T WAVE
POLARITY

O melhor movimento feminino ainda é o dos quadris

El mejor movimiento femenino todavia es el del los cuadriles

The best women's movement is still hip movement

**Raimundo Barbosa Barros MD. Nickname: “the Fox” Coronary Center Hospital de
Messejana Dr. Carlos Alberto Studart Gomes Fortaleza-Ceará-Brazil**

**Comments: Andrés Ricardo Pérez-Riera MD PhD Faculdade de Medicina do ABC-Santo
André SP Brazil**

Estimados colegas foristas: Paciente del sexo femenino, 78 años, con queixa de dor precordial em aperto, sem irradiação não desencadeada pelo esforço.

História de hipertensão e diabetes de longa data. Tabagista por 20 anos, parou há 14 anos. Nega dislipidemia.

Refere implante de marca-passo em abril desse ano devido a quadros repetidos de síncope.

Faz uso dos seguintes fármacos: captopril, isordil, atenolol, amitriptilina.

Exame físico sem alterações importantes. Pergunta: fenômeno de Chatterjee? Inversão isquêmica da onda T?

Mujer, 78 años, con dolor en el pecho opresivo no desencadenado por esfuerzo y sin irradiación.

Hipertensión arterial y diabetes mellitus de largo tiempo. Fumó durante 20 años, Dejó el vicio hace 14 años. Niega dislipidemia.

Marcapaso implantado en abril de este año por eventos sincopales repetitivos.

Medicamentos en uso: captopril, nitrato, atenolol, amitriptilina.

Examen físico sin cambios importantes. Pregunta: fenómeno de Chatterjee?

Inversão isquêmica da onda T?

Dear forum colleagues : Female 78yo complain of oppressive chest pain without irradiation Not effort related. History of hypertension and type 2 diabetes of long standing. Smoking for 20 years, stopped 14 years ago. She denied dyslipidemia.

Refers pacemaker implant (Dual-Chamber Pacemaker) in April of this year due to repeated syncope episodes.

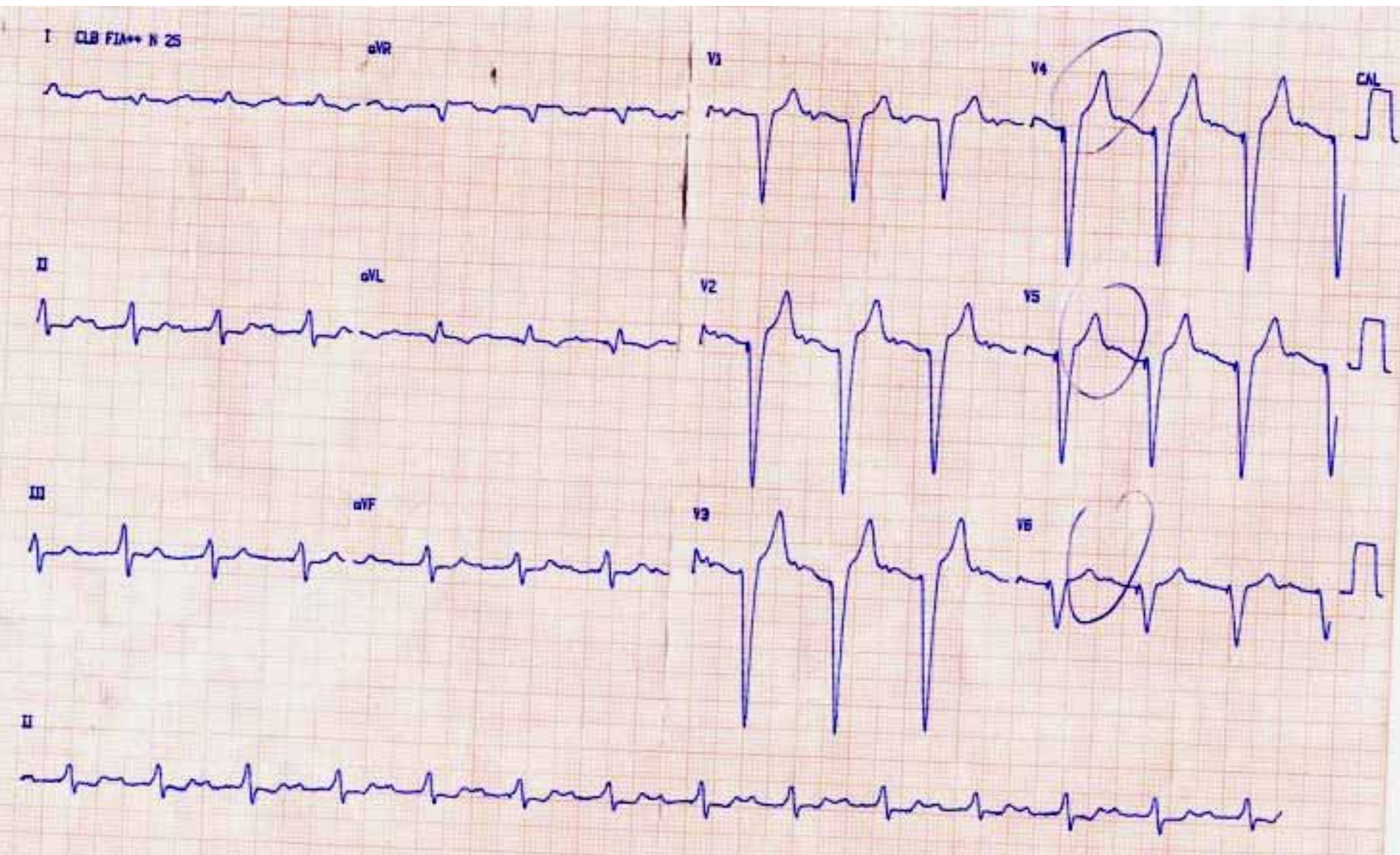
She use of the following drugs: captopril, Isordil, atenolol, amitriptyline.

Physical examination revealed no major change

Questions: Chatterjee phenomenon? Ischemic-related T-wave inversion? Raimundo

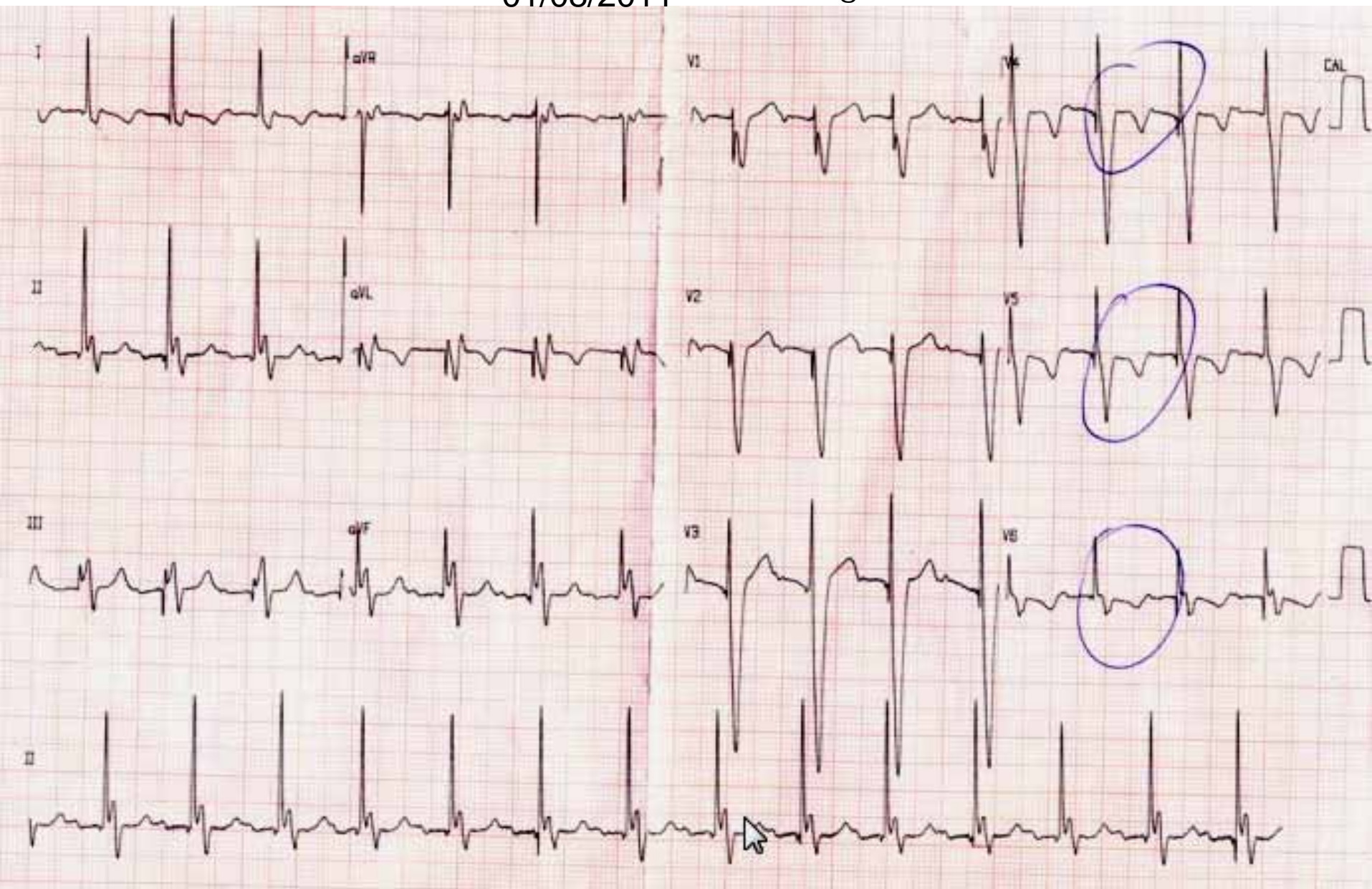
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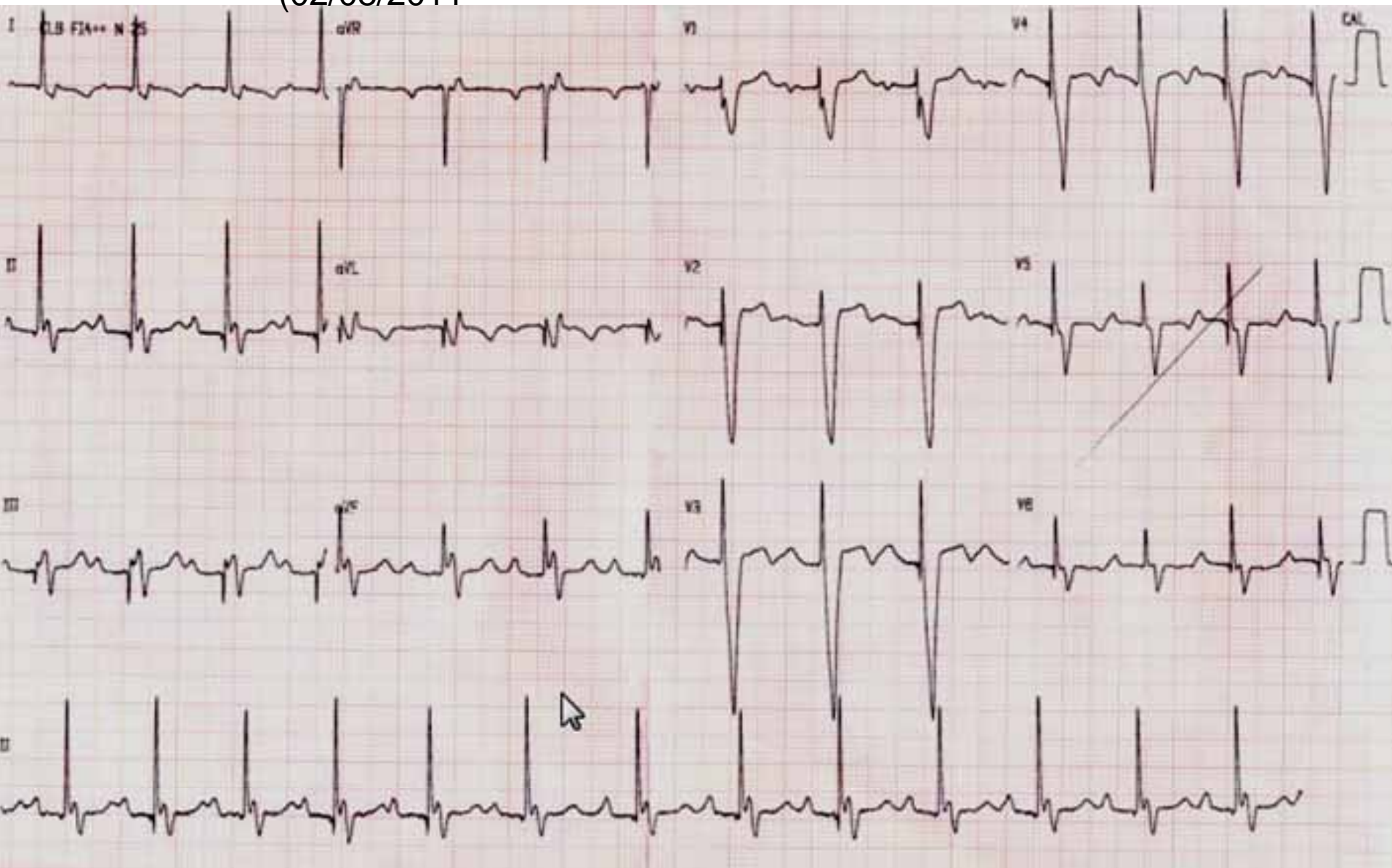
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The Thinker is a bronze and marble sculpture by Auguste Rodin, whose first cast, of 1902, is now in the Musée Rodin in Paris; there are some twenty other original castings as well as various other versions, studies, and posthumous castings. It depicts a man in sober meditation battling with a powerful internal struggle. It is often used to represent philosophy. In the present case we need to think a lot!!!!

François-Auguste-René Rodin The Thinker

Amigos del foro y en especial Raimundo:

Supongo que todos pensareis que los cirujanos no tenemos humildad, lo cual me incapacita para dar mi humilde opinión, así que solo daré mi opinión. Ahí va:

Los tres trazados presentan ritmo de marcapasos aparentemente en modo VDD con intervalo PR muy prolongado. La diferencia entre el primero y los dos siguientes (haciendo abstracción de los cambios de repolarización) se manifiesta en el tamaño de la espiga ventricular, lo que me hace suponer que existe cambio de polaridad de bipolar a unipolar. En ausencia de reprogramación, lo más probable es que este cambio se haya producido de forma automática por detección de altas impedancias en alguno de los dos polos del electrodo.

Además la morfología de los complejos del primer ECG (llamesmole normal o no patológico) con ausencia de BCRI típico e imágenes rS en V5-V6 me hace pensar que la punta del electrodo está alojada en zona de septo apical de VD y probablemente penetrada en el mismo.

La aparición de dolor precordial y cambios de polaridad me hacen pensar en que el electrodo ha perforado con su punta distal a espacio pericárdico y solo estimula con el polo proximal. Los cambios de repolarización junto con el dolor serían compatibles con la pericarditis consiguiente.

Descarto un fenómeno de Chatterjee porque requiere ausencia de estimulación para producirse y en este caso el estímulo de marcapasos ventricular es constante.

Un saludo a todos.

Antonio D. Jimenez-Ramos

Cirujano Cardiovascular

Madrid, España

Querido Dr Jimenez-Ramos muchas gracias por su inteligente análisis. Cuando el cateter esta localizado en el ápice de VD el ECG muestra patrón CR1 con anormal desvío del eje a la izquierda entre -30 y -90 en mas de 90% de los casos. Se registra una deflexión positiva en I y aVL. La derivación V6 es variable desde que frecuentemente muestra una deflexión terminal negativa lo cual simplemente indica que la activación fué superior.(1). En este caso el patrón de I y aVL no es R puro es qr.

Dear Dr Jimenez-Ramos: Thank very much for your clever analysis. When the catheters are placed in the right ventricular apex the ECGs show a LBBB pattern with abnormal left axis deviation between -30 and -90 in more than 90% of cases. A predominant positive deflection is recorded in I and aVL. Lead V6 is variable since it frequently show a terminal negative deflection which simply indicated superior final activation.(1) In the present case the QRS pattern is not R wave or predominant R wave. It is qr.

1.Castellanos Jr, Ortiz J, Pastis N et al. THE VECTORCARDIOGRAM OF DIFFERENT PACEMAKER SITES. In Xth International Vectorcardiography Symposium 1971. North Holland Publishing Company Amsterdam pp 304-313.

Andrés.

Querido Andrés: La referencia aportada carece de valor para analizar posición del catéter en el VD porque precede a la era del implante en el tracto de salida del VD.

Hay numerosas buenas citas al respecto, y creo seria conveniente leer las actualizadas.

No es que reniegue de citas madre, pero en este tópico el avance ha sido tan grande que no puede desconocerse que el implante en el septo es la posición elegida en la mayoría de los laboratorios en la actualidad. Lo saludo con distinguida cortesía.

Es la primera vez que oigo a un cirujano hablando de humildad y dándole importancia al tema: en hora buena Dr JR. AB Adrian Baranchuk

Estimado Adrian: Perdoname pero la posición del cateter en la punta del VD ocasiona un extremo desvio del eje del QRS arriba de -30° dando R grandes en torre en las izquierdas altas I y aVL que este caso no tiene. Este concepto es un paradigma consolidado. Pone a funcionar tu cabeza. La estimulación en la punta del VD se procesa = que el LBBB natural que activa el corazon secuencialmente a partir de la rama derecha que termina en la punta del VD en la base del musculo papilar de la tricuspide. Dando siempre R pura en torre en I y aVL. Apenas en la region apical del VI o lateral baja (V5-V6) es posible registrar RS o Rs.

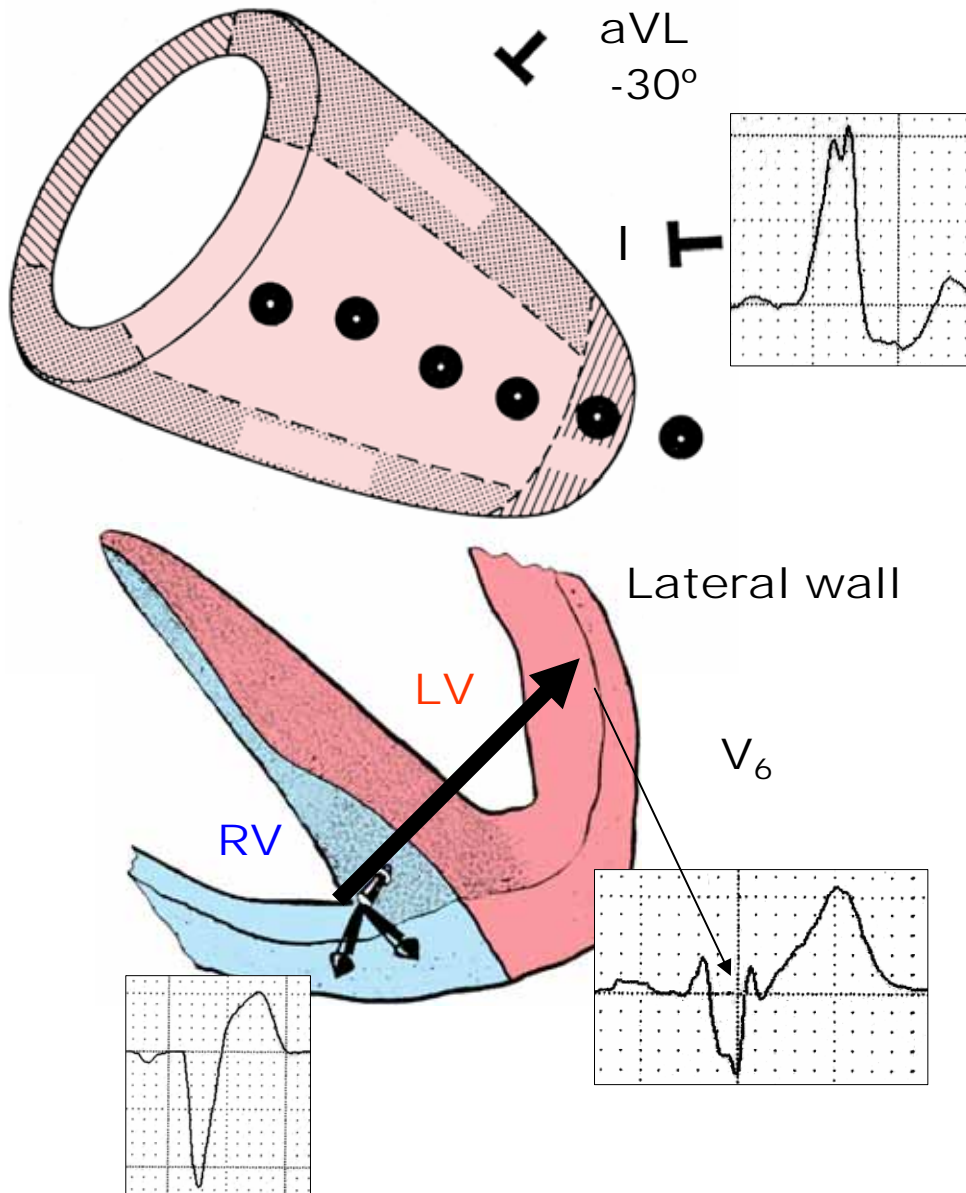
Ademas te comunico que no precede a la posicion en el tracto de salida. A este respecto los autores en este antiguo trabajo del 71 escriben literalmente asi:

Right ventricular outflow tract pacing:...*”several patients of our series were obtained during temporary pacing while the electrodes were close to the pulmonary valves The ECG showed a LBBB patter manifested by negative deflections in V1 and positive in V6 However, the AQRS was deviated slightly to the right around $+110^{\circ}$ In the spatial VCG the maximal QRS vector was located posteriorly to the right , and either slightly superiorly or inferiorly, These was a uniform delay of the loops The later had clockwise rotation in the horizontal plane and counterclockwise wise rotation in the frontal plane, The most constant finding during RV pacing was the negative deflection in V1”.*

Castellanos divide las morfologias ECG/VCG del pacing en 5 grupos que caracterizan con claridad meridiana:

- 1. Right ventricular apical stimulation**
- 2. Stimulation form the mid-outflow tract of the right ventricle**
- 3. Right ventricular outflow tract pacing**
- 4. Left ventricular pacing**
- 5. Left ventricular stimulation during trans venous pacing consequence of penetration of the catheter into a coronary vein running downward over the inferior surface.**

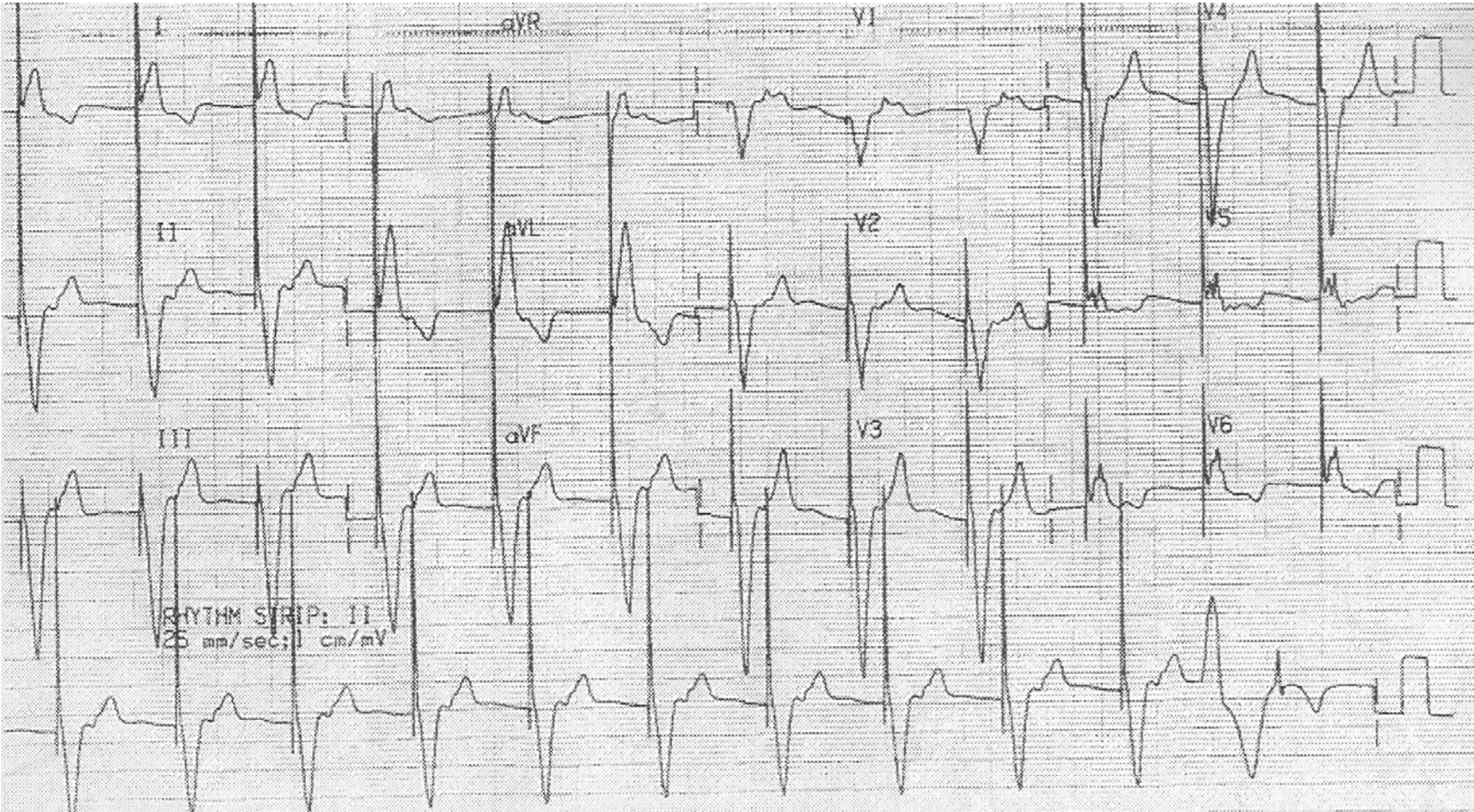
RIGHT VENTRICULAR APICAL STIMULATION AND QRS PATTERNS



Altered connexin expression was first described in the early-activated region with local reduction in conduction velocity. Connexin43(Cx43), the main gap junction protein in the ventricular myocardium plays an important role in cell-to-cell coupling. Altered Cx43 expression causes conduction slowing, enhances repolarization gradients and increases susceptibility to arrhythmia in HF.(1) Cx43 expression was examined in the late-activated region of the canine dyssynchronous pacing induced HF model.(2) In this model, experimental LBBB was used to examine remodeling in early-activated (septum) and late-activated ventricular regions (lateral wall). In late-activated regions there was no reduction in expression of Cx43, however, redistribution of connexins to the lateral wall of the myocytes termed “lateralization” was observed with reduced conduction velocity. Therefore, altered connexin expression with regional changes in conduction likely plays a role in enhancing regional repolarization gradients observed in memory. To summarize, the pattern of sarcolemmal ion channel and connexin remodeling are dependent on the anatomical location of the myocardium remodeled with respect to the origin of altered activation.

1. Poelzing S, Rosenbaum DS. Altered connexin43 expression produces arrhythmia substrate in heart failure. *Am J Physiol Heart Circ Physiol.* 2004 Oct;287(4):H1762-70.
2. Spragg DD, Akar FG, Helm RH, et al. Abnormal conduction and repolarization in late-activated myocardium of dyssynchronously contracting hearts. *Cardiovasc Res.* 2005 Jul 1;67:77-86.

VVI pacemaker with ventriculoatrial conduction that shows retrograde P waves at the onset of T wave, and clearly negative in the inferior wall. This is by far the most common type of pacemaker. It senses spontaneous ventricular impulses and paces the ventricles only when needed.



Case Dr Elisabeth Kaiser MD InCor SP Brazil

El primer se ve el ritmo de marcapaso D2,D3, con QRS bizarro característico de Wolf Parkinson White con ondas T previas a una TV. V4,V5,V6.

Segundo trazo D2,D3,aVL,aVF. con isquemia y onda T con fenómeno de R en T. onda T invertida en V4,V5,V6 Con el DII largo rumbo a TV y muerte súbita.

Tercer trazo DII,DIII,aVL,aVF persiste la isquemia y el fenómeno R en T en V3,V4,V5 ritmo agonal con 1 extrasístoles V5,V6 aisladas. Llama la atención el patrón del QRS en V2,V3,V4 .

Mis Saludos.

Gregorio Maslivar

Esta es la opinion del Profesor Bory Surawicz Profesor Emerito de la Universidad de Indiana.

Is there anything more than post-pacing T-wave changes? In the dictionary: radiation is radiacion. I do know what irradiation is?

Regards Borys

Thank very much dear Borys for your appropriate correction. Raimundo change radiation by radiating:

ELDERLY WOMAN WITH OPRESSIVE CHEST PAIN CHARACTER AT REST, NOT RADIATING IMPLANTED PACEMAKER AND DINAMIC CHANGES OF THE T WAVE POLARITY

Estimado Dr Raimundo: recibia el atenolol y la amitriptilina previo a la colocacion del marcapasos? Se encuentra en tratamiento con nitratos y BB. Supongo fue interpretada como una paciente coronaria, tenia estudios evocadores de isquemia previa a la decison de colocar el MCP definitivo?. El modo en que impresiona funcionar es VVD con captura 1:1 de los latidos sinusales sensados pero me llama la atencion la programacion impresiona respuesta en frecuencia pero responde a 98 por min y en ECG posteriores a 100 por min. La paciente es coronaria (evidenciado por la inversion de la onda T en precordiales izquierdas) al encontrarse en reposo con esta frecuencia es de esperar padezca de crisis anginosas, y me corregira luego en esto pero en los trazados posteriores la p cambia de morfologia y el tiempo AV se acorta a 0,22 seg e igualmente continua con capturas del marcapasos. Lo que impresionana son latidos de fusion.

Seria interesante observar un ECG con el marcapasos inhibido.

Contraindicaciones del la Amitriptilina: IAM reciente: ante el riesgo de producir bloqueo cardiaco. Precauciones: Alteraciones cardiovasculares (angina de pecho, arritmias cardiacas, hipertensión, insuficiencia cardiaca congestiva, insuficiencia coronaria): aumenta el riesgo de arritmias, bloqueo cardiaco, insuficiencia cardiaca congestiva, infarto de miocardio o accidente cerebrovascular. Ocasionalmente (1-9%): somnolencia; hipotensión ortostática y taquicardia especialmente en ancianos, arritmia cardiaca, depresión miocárdica, cambios en el electrocardiograma (ECG) (prolongación en los intervalos QT y QRS); erupciones exantemáticas, leucopenia, agranulocitosis, ictericia colestática y aumento de peso. **USO EN ANCIANOS** Los ancianos pueden ser más sensibles a los efectos anticolinérgicos, delirio anticolinérgico, hipotensión y sedación. Estos efectos pueden dar lugar a un aumento de la ansiedad conduciendo posiblemente a un aumento innecesario de la dosis. Si además existe enfermedad cardiovascular, aumenta el riesgo de problemas en la conducción, arritmias, taquicardia, accidente cerebrovascular, insuficiencia cardíaca congestiva o infarto de miocardio. Los ancianos presentan enlentecimiento del metabolismo y/o de la excreción. Se recomienda una reducción de la dosificación e incrementar la dosis más gradualmente, así como un especial control clínico.

Saludos Martin Ibarrola

Dear Andres,

**Besides T wave inversion in the LV leads, the QRS morphology has changed dramatically-
the wide QRS with late onset sharp S wave is rare.**

Hope to learn the good explanations from YOU and other ECG Pros.

Thank you very much!

Li

Ours final conclusions

The initial differential diagnosis in this old woman included:

1. **Acute myocardial ischaemia due to plaque rupture:** Acute myocardial necrosis is excluded by repeated analysis of heart enzymes, which never exceeded the normal range.
2. **Coronary embolism arising from the large left atrium:** mainly in cases of AF.
3. **Penetration of the ventricular lead (which had passive fixation):** Ventricular lead penetration is excluded if absence of a pericardial effusion on repeat echocardiography.
4. **Drugs that cause repolarization abnormalities:** e.g. digitalis, were not being given at that time.
5. **"T-wave memory" or cardiac memory phenomenon with simultaneous non-cardiac pain:** Cardiac memory describes the phenomenon whereby the T-wave abnormalities that result from a change in the direction of cardiac activation, as during ventricular pacing, persist for a while after the end of pacing. Transient repolarization abnormalities consistent with cardiac memory phenomenon. Although the existence of cardiac memory has been known for many years, there is still limited information regarding its physiological significance and clinical implications. Clinicians do, however, need to be aware that this electrical curiosity, also termed Chatterjee phenomenon(1), can imitate acute myocardial ischaemia.

1. **Chatterjee K, Harris A, Davies G, Leatham A. Electrocardiographic changes subsequent to artificial ventricular depolarization. *Br Heart J* 1969; 31: 770-9.**

Cardiac memory is characterized by persistent but reversible T-wave changes on the surface ECG induced by an abnormal electrical activation pattern after a period of abnormal ventricular activation. : the reported stimuli include:

- Ventricular pacing Rosenbaum et al (1;2) noted that alteration in activation pattern of the ventricle was a more important trigger than change in HR in inducing T-wave changes.
- Intermittent Left Bundle Branch Block (2;3)
- Periods of pre-excitation observed in Wolff-Parkinson-White syndrome(4), and
- Episodes of tachycardia(5;6).

This poorly understood process occurs when the heart resumes a sinus rhythm after a period of abnormal depolarization. The precordial leads in these patients will demonstrate alarmingly deep, symmetrical T-wave inversions.

Traditionally, to observe Cardiac memory, normal ventricular activation had to be restored, limiting the exploration of this phenomenon in clinical practice.

1. Rosenbaum MB, Blanco HH, Elizari MV, et al. Electronic modulation of the T wave and cardiac memory. *Am J Cardiol* 1982;50: 213-222.
2. Rosenbaum MB, Elizari MV, Lazzari JO, et al. The mechanism of intermittent bundle branch block: relationship to prolonged recovery, hypopolarization and spontaneous diastolic depolarization. *Chest* 1973;63: 666-677.
3. Byrne R, Filippone L. Benign persistent T-wave inversion mimicking ischemia after left bundle-branch block--cardiac memory. *Am J Emerg Med*. 2010 Jul;28:747.e5-6.
4. Kalbfleisch SJ, Sousa J, el-Atassi R, et al. Repolarization abnormalities after catheter ablation of accessory atrioventricular connections with radiofrequency current. *J Am Coll Cardiol* 1991;18: 1761-6.
5. Kernohan RJ. Post-paroxysmal tachycardia syndrome. *Br Heart J* 1969;31: 803-806.
6. Currie GM. Transient Inverted T Waves After Paroxysmal Tachycardia. *Br Heart J*. 1942 Oct;4:149-152.

Recently, Shvilkin et al(1) from Israel proved that cardiac memory can be detected during continuous aberrant activation and to establish factors affecting its magnitude using a vectorcardiographic technique. The authors studied 16 nonpacemaker-dependent patients (11 male, age 72 +/- 8 years, mean +/- SD) undergoing pacemaker/internal cardioverter-defibrillator implantation were paced in DDD mode with a short atrioventricular (AV) delay for 7 days to induce cardiac memory. ECGs were acquired during AAI and DDD pacing at a constant rate before and after cardiac memory induction. Dower transform-derived VCGs were reconstructed and analyzed. T vector during AAI pacing changed in both magnitude (baseline, 0.26 +/- 0.10 mV; Day 7, 0.39 +/- 0.13 mV, $P < .01$) and direction aligning with the paced QRS vector (baseline DDD QRS - AAI T angle 125 degrees +/- 36 degrees; Day 7, 39 degrees +/- 21 degrees, $P < .01$). During DDD pacing, there was no change in T-vector direction, but T amplitude decreased (baseline, 1.06 +/- 0.32 mV; Day 7, 0.71 +/- 0.26 mV, $P < .01$). Cardiac memory measured as T-vector peak displacement (TPD) was identical in AAI and DDD mode (TPD 0.46 +/- .017 mV and 0.46 +/- 0.17 mV, respectively). Individual cardiac memory magnitude correlated with QRS/T-vector amplitude ratio during DD D pacing at baseline ($r = 0.90$).

The authors concluded that cardiac memory can be reliably shown during continuous ventricular pacing, expanding its application to situations in which abnormal ventricular activation persists. Its magnitude is determined by the QRS/T-amplitude ratio of the ventricular paced beat.

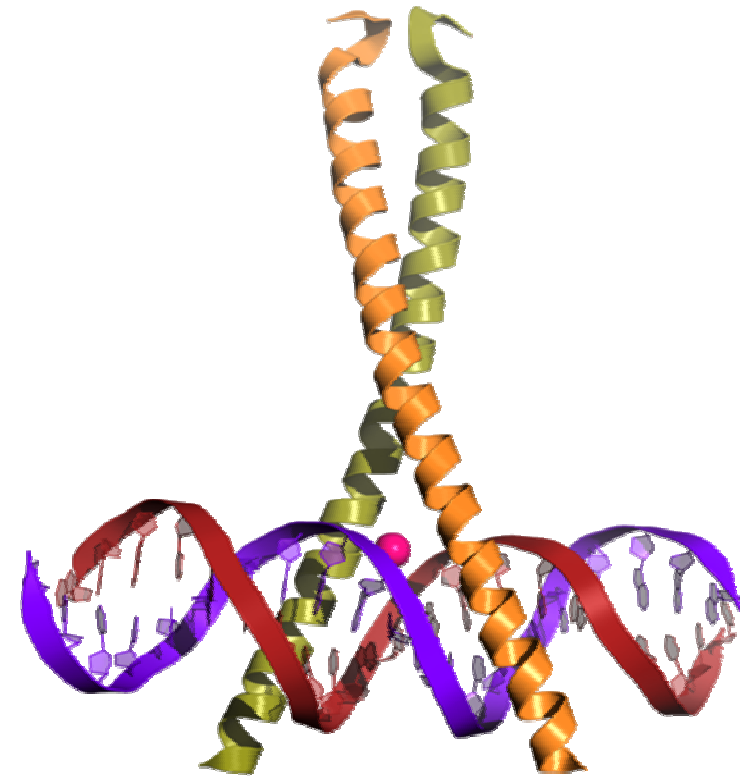
- 1. Shvilkin A, Bojovic B, Vajdic B, et al. Vectorcardiographic determinants of cardiac memory during normal ventricular activation and continuous ventricular pacing. Heart Rhythm. 2009 Jul;6:943-948.**

The extent and the direction of T-wave deviation depend on the duration and the direction of the abnormal electrical activation; the phenomenon can persist for several weeks.

The underlying cellular mechanisms of cardiac memory are unclear, but existing data point to modification of specific potassium channels and changes in the phosphorylation status of the cAMP responsive element binding protein (CREB)(1). CREB (cAMP response element-binding) is a cellular transcription factor. It binds to certain DNA sequences called *cAMP response elements* (CRE), thereby increasing or decreasing the transcription of the downstream genes. CREB was first described in 1987 as a cAMP-responsive transcription factor regulating the somatostatin gene. Genes whose transcription is regulated by CREB include: *c-fos*, the neurotrophin BDNF (Brain-Derived Neurotrophic Factor), tyrosine hydroxylase, and many neuropeptides (such as somatostatin, enkephalin, VGF, and corticotropin-releasing hormone). CREB is closely related in structure and function to CREM (cAMP response element modulator) and ATF-1 (activating transcription factor-1) proteins. CREB proteins are expressed in many animals, including humans.

CREB has a well-documented role in neuronal plasticity and long-term memory formation in the brain and heart(2).

1. Patberg KW, Plotnikow A, Giannulin R, *et al.* Cardiac memory is associated with alterations in the cAMP responsive element binding protein and its phosphorylation form. *PACE* 2001;24: 645.
2. Ozgen N, Lau DH, Shlapakova IN, *et al.* Determinants of CREB degradation and KCHIP2 gene transcription in cardiac memory. *Heart Rhythm*. 2010 Jul;7:964-970.



CREB (top) is a transcription factor capable of binding DNA (bottom) and regulating gene expression.

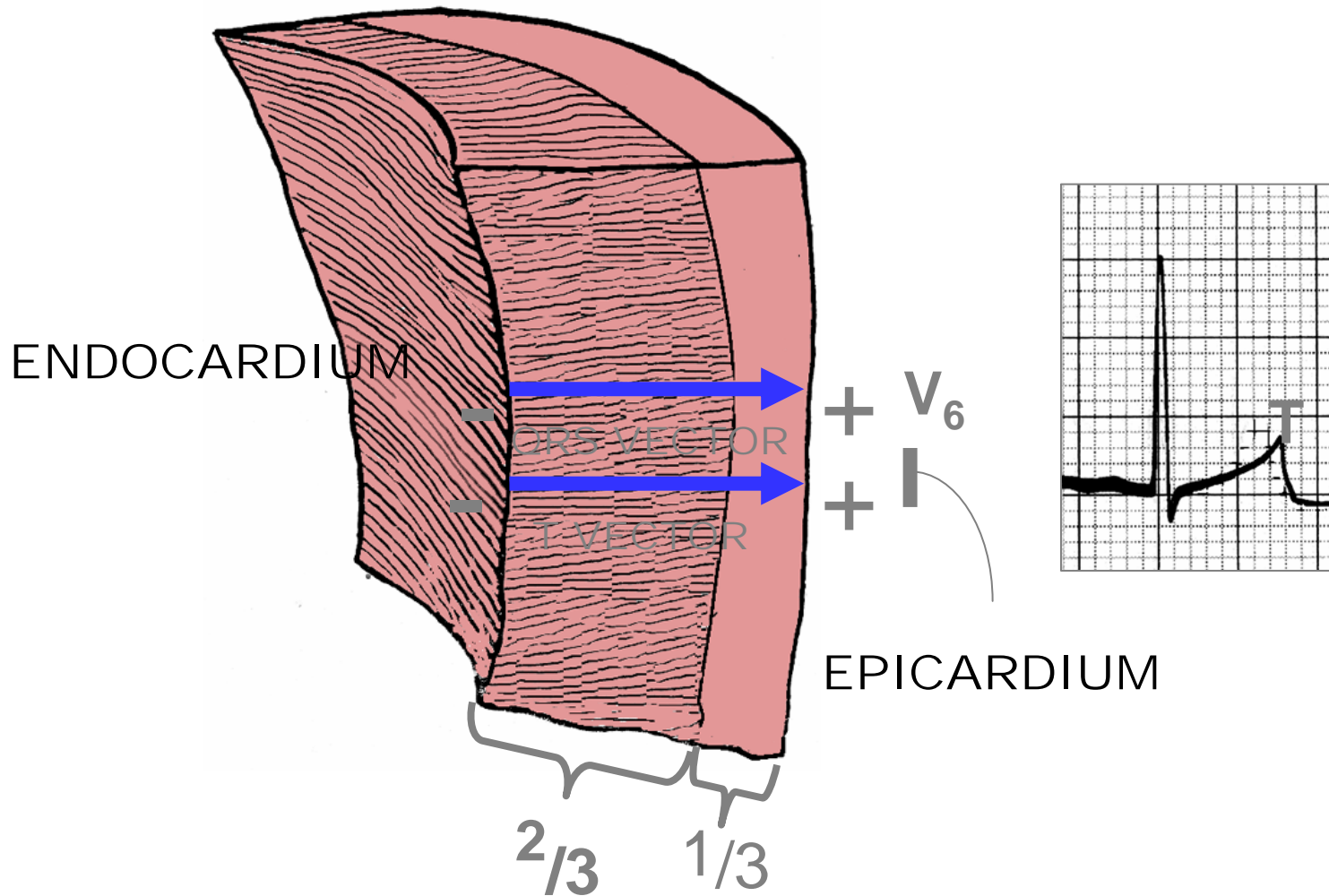
Left ventricular pacing to induce cardiac memory in dogs results in a decreased transient outward K current (I_{to}) and reduced mRNA and protein of the I_{to} channel accessory subunit, KChIP2. The KChIP2 decrease is attributed to a decrease in its transcription factor, cyclic adenosine monophosphate response element binding protein (CREB). Ozgen et al(1) studied the mechanisms responsible for the CREB decrease that is initiated by left ventricular pacing.

Cardiac memory was quantified as T-wave vector displacement in 18 left ventricular pacing dogs. In 5 dogs, angiotensin II receptor blocker, saralasin, was infused before and during pacing. In 3 dogs, proteasomal inhibitor, lactacystin, was injected into the left anterior descending artery before left ventricular pacing. Epicardial biopsy samples were taken before and after left ventricular pacing. Neonatal rat cardiomyocytes (NRCM) were incubated with H₂O₂ (50 micromol/l) for 1 hour with or without lactacystin. Left ventricular pacing significantly displaced the T-wave vector and was associated with increased lipid peroxidation and increased tissue angiotensin II levels. Saralasin prevented T-vector displacement and lipid peroxidation. CREB was significantly decreased after 2 hours of left ventricular pacing and was comparably decreased in H₂O₂-treated NRCM. Lactacystin inhibited the CREB decrease in left ventricular pacing dogs and H₂O₂-treated NRCM. Left ventricular pacing and H₂O₂ both induced CREB ubiquitination, and the H₂O₂-induced CREB decrease was prevented by knocking down ubiquitin.

The authors conclude that left ventricular pacing initiates myocardial angiotensin II production and reactive oxygen species synthesis, leading to CREB ubiquitination and its proteasomal degradation. This sequence of events would explain the pacing-induced reduction in KChIP2, and contribute to altered repolarization and the T-wave changes of cardiac memory(1).

- 1. Ozgen N, Lau DH, Shlapakova IN, et al. Determinants of CREB degradation and KChIP2 gene transcription in cardiac memory. Heart Rhythm. 2010 Jul;7:964-970.**

VENTRICULAR REPOLARIZATION: T VECTOR



Representation of ventricular repolarization (vector T), where we observe that depolarization (QRS) and repolarization (T wave) have the same direction, and therefore, similar polarities of QRS and T wave.

VENTRICULAR REPOLARIZATION

- 1) Repolarization is an electrical phenomenon opposite to depolarization.
- 2) In the ventricles, repolarization starts in the epicardium towards the endocardium and from the base to the point.
- 3) It occurs during mechanical systole, a fact that explains the inversion of the sequence regarding depolarization.
- 4) Repolarization (vector T), is electrically inverse to depolarization.
- 5) The vector that is represented begins in the epicardium and it moves backwards, pointing its positive end (+) towards this region and thus, it gains positive charges towards the endocardium, where the origin (-) of the vector is located.

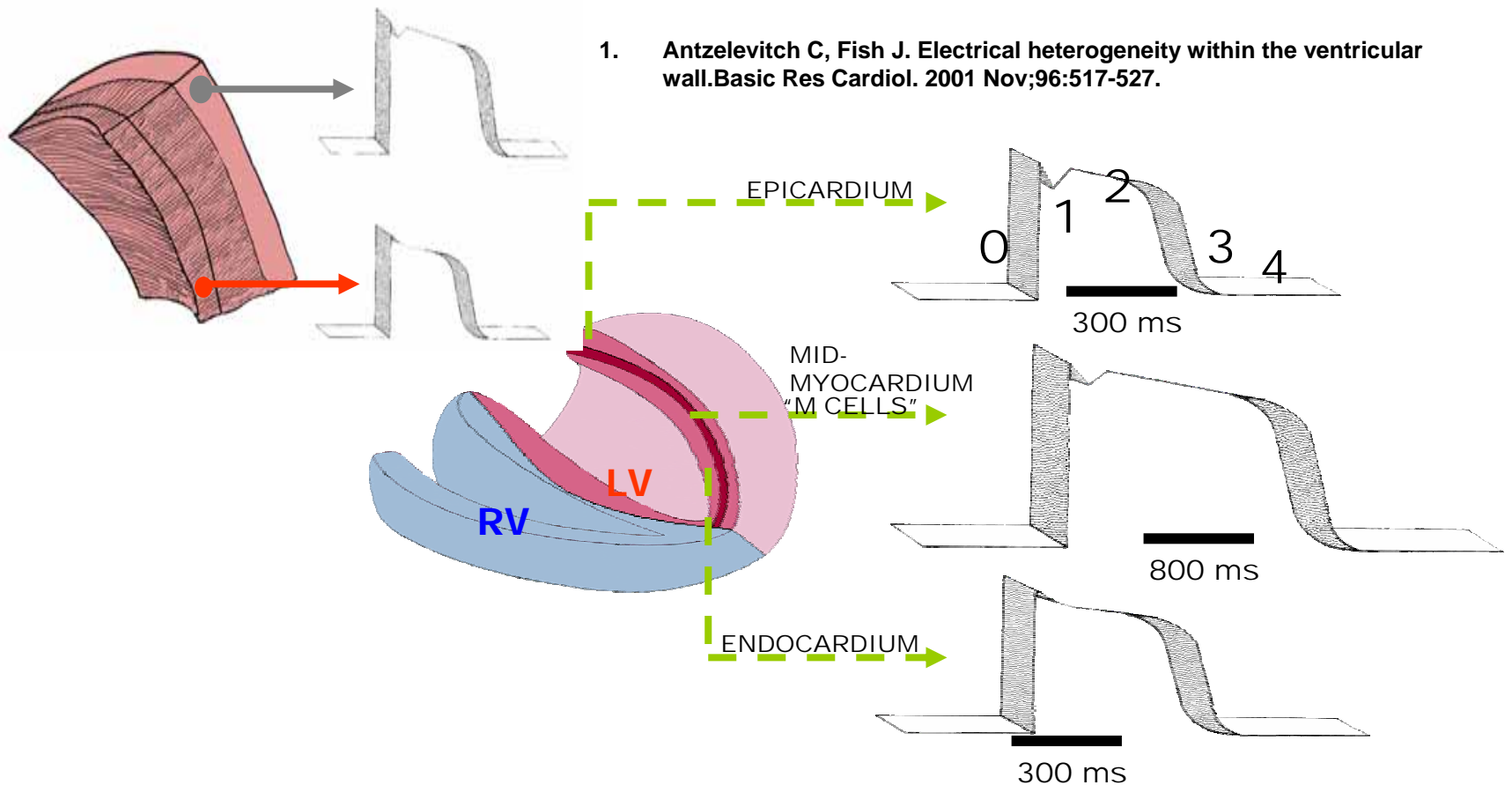
Explanation of the phenomenon of ventricular repolarization: T vector.

The electrophysiological remodeling following altered activation is characterized by distinct changes in regions proximal (early-activated) versus distal (late-activated) to the site of altered activation. The early-activated region exhibits marked attenuation of epicardial phase 1 notch due to reduced expression of the transient outward potassium current (I_{to}). This is attributed to electrotonic changes during altered activation, and angiotensin-mediated regulation of Kv4.3 (the pore-forming alpha subunit responsible for I_{to}).

The late-activated region exhibits the most significant action potential (AP) prolongation due to markedly increased mechanical strain through a mechano-electrical feedback mechanism. Consequently, regionally heterogeneous AP remodeling occurs following altered activation. This enhances regional repolarization gradients that underlie the electrophysiological basis for T-wave memory. Further, recent clinical studies highlight detrimental consequences of altered activation including worsening mechanical function and increased susceptibility to arrhythmias. Future studies to identify molecular mechanisms that link electrotonic and mechanical strain-induced changes to cellular electrophysiology will provide important insights into the role of altered activation in regulating cardiac repolarization and arrhythmogenesis.

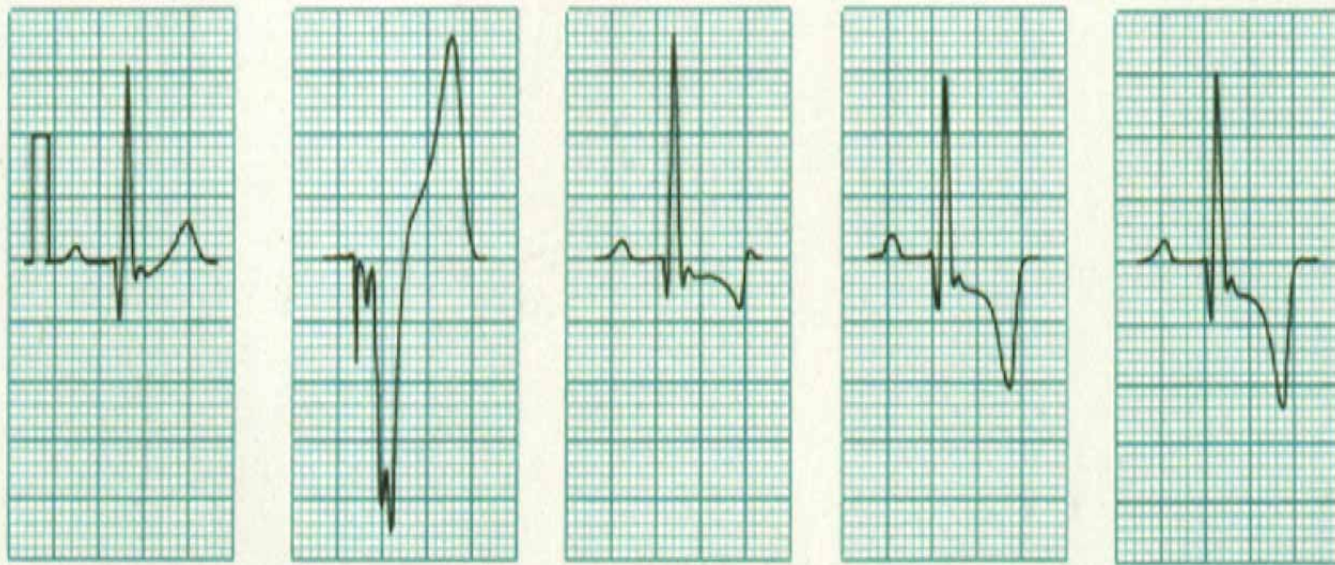
1. **Jeyaraj D, Ashwath M, Rosenbaum DS. Pathophysiology and clinical implications of cardiac memory. *Pacing Clin Electrophysiol.* 2010 Mar;33:346-352.**

The origin of the normal upright T-wave has been controversial. The myocytes that span the transmural surface of the LV exhibit the largest ventricular repolarization gradient in the canine LV.(1).This is due to significantly longer AP in M cells compared to the shorter epicardial cells. Therefore, the direction of repolarization which begins in epicardial cells is opposite to the direction of depolarization. These opposing gradients provide the most likely current electrophysiological basis for the normal upright T-wave.



The thickness of the ventricular wall is formed by three functional layers, with different APs. In the depth of the middle layer we find M cells, which have a subpopulation of cells with a great conduction velocity and electrophysiological properties of their own, which are very relevant in the pathophysiology of long and short QT syndromes and T memory.

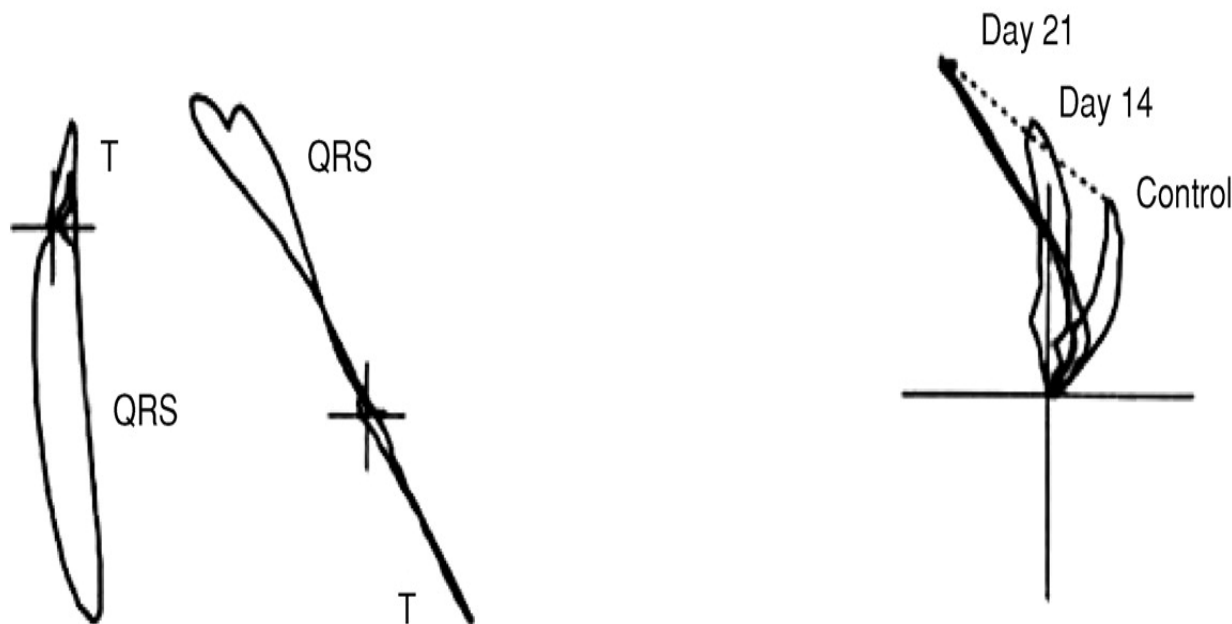
Evolution of cardiac memory



Control Ventricular pacing Day 7 Day 14 Day 21

Upper panels show canine ECG during control sinus rhythm, during ventricular pacing at about 5% faster than sinus rate, and – a few minutes after returning to sinus rhythm – on days 7, 14 and 21 of pacing. Note that the QRS complex is inverted during ventricular pacing and that the T wave in the subsequent panels in sinus rhythm becomes progressively inverted, following the direction of the paced QRS complex.

1. Rosen MR, Cohen IS. Cardiac memory ... new insights into molecular mechanisms. *J Physiol.* 2006 Jan 15;570:209-218.



The two left bottom panels show the VCG of the same dog in control (sinus rhythm) and during ventricular pacing. Note the change in vector shape, angle and amplitude of the QRS complex. The right lower panel shows an enlargement of the T wave vector during control sinus rhythm and in sinus rhythm on days 14 and 21. Note that the T wave vector has moved in the direction of the paced QRS, and also shows an increased amplitude. Modified from Shvilkin *et al.* (1998).

THE HEART REMEMBERS

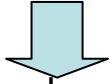
Ventricular pacing



Altered activation



Altered stress/strain



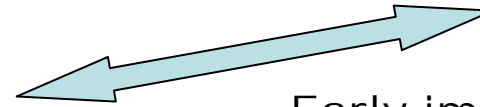
Signal transduction cascade



New Protein Synthesis



Serine/threonine kinase



Early immediate regulatory gene reduction



Effector protein phosphorylation



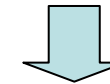
Altered Channel function



Altered Gradient



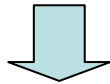
Short term memory



Altered expression of late phase
Channel structural protein



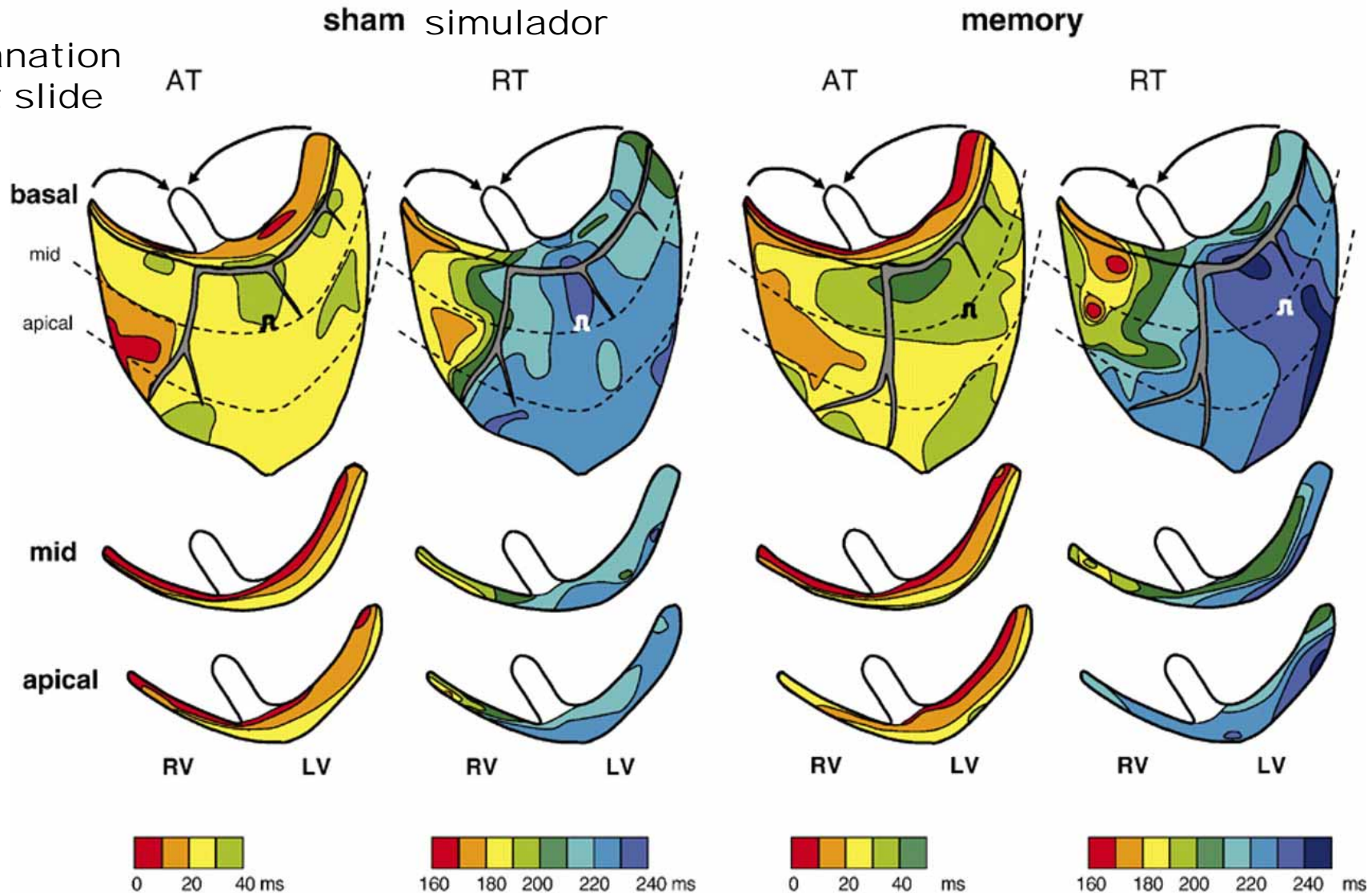
Altered channel



Long term memory

Long-term cardiac memory in canine heart is associated with the evolution of a transmural repolarization gradient

Explanation
next slide



Example of the three-dimensional distribution of transmural and epicardial activation times (AT) and repolarization times (RT) in the hearts of one sham dog and one memory dog during atrial pacing. Transmural AT and RTs are depicted at three levels: basal, middle (mid) and apical. RV: right ventricle; LV left ventricle. Lines are isochrones. Colors indicate isochronal classes (scale in ms shown below). Site of stimulus electrode is indicated by stimulus sign. Note that LV RTs are delayed in memory relative to sham, and that transmural LV RT gradients are larger.

Cardiac memory was induced by three weeks of AV-sequential pacing at the anterior free wall of the left ventricle (LV), midway between apex and base in 5 dogs. In 4 sham controls a pacemaker was implanted but ventricular pacing was not performed. At 3 weeks, unipolar electrograms were recorded (98 epicardial, 120 intramural and endocardial electrodes) during atrial stimulation (cycle length 450 ms). Activation times (AT) and repolarization times (RT) were measured and activation recovery intervals (ARIs) calculated. Cardiac Memory was associated with 1) deeper T waves on ECG, with no change in QT interval; 2) longer activation time at the site of stimulation in Cardiac Memory (29.7 ± 1.0 , $X \pm \text{SEM}$) than sham (23.9 ± 1.3 ms $p < 0.01$); 3) an LV transmural gradient in repolarization time such that repolarization at the epicardium terminated 12.4 ± 2.4 ms later than at the endocardium ($p < 0.01$), in contrast to no gradient in shams (2.7 ± 4.2 ms); in memory dogs, the repolarization time gradient was greatest at sites around the pacing electrode varying from 13.1 ± 2.3 ms to 25.5 ± 3.8 ms; 4) more negative left ventricular potentials at the peak of the body surface T wave (-4.9 ± 0.8 vs -2.2 ± 0.4 mV; $p < 0.05$) but no altered right ventricular epicardial T-wave potentials. ARIs did not differ between groups. Right ventricular activation was delayed but was not associated with altered repolarization because of compensatory shortening of the right ventricular ARIs.

The authors concluded that cardiac memory-induced T-wave changes are caused by evolution of transmural repolarization gradients manifested during atrial stimulation that are maximal near the site of ventricular pacing.

- 1. Coronel R, Opthof T, Plotnikov AN, et al. Long-term cardiac memory in canine heart is associated with the evolution of a transmural repolarization gradient. *Cardiovasc Res.* 2007 Jun 1;74:416-425.**

Chiale et al(1) tested the hypothesis that in the presence of abnormal T waves (TW), short periods of tailored ventricular pacing (VP) can be followed by normalization of ventricular repolarization.

- Control group 10 patients with normal TW**
- Study group: 18 patients with abnormal TW.**

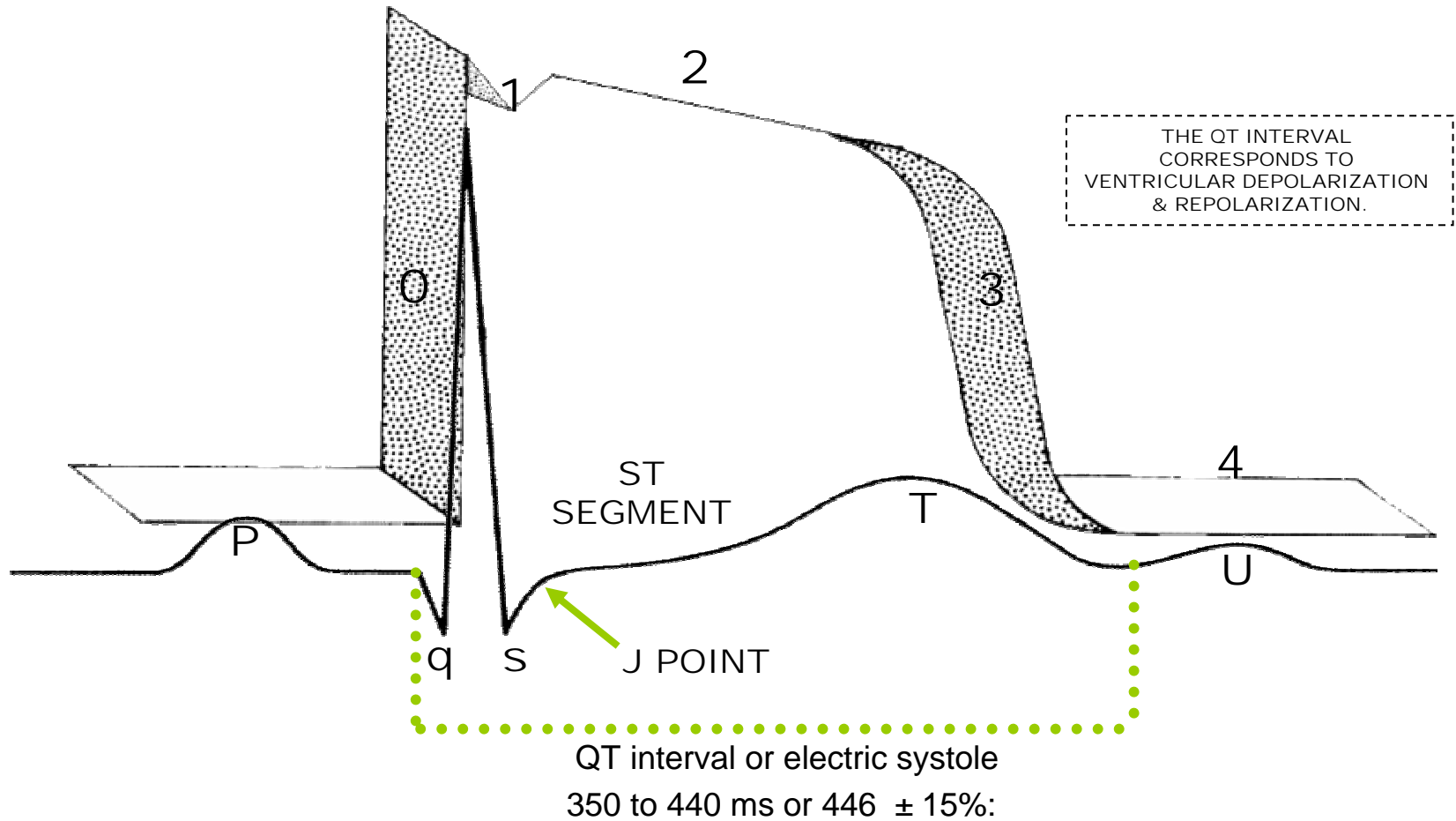
Underwent 15 min of VP at a cycle length of 500 ms. In the control group, VP was performed from the right ventricular apex, and in the study group from right or left ventricular sites that resulted in paced QRS complexes of opposite polarity to that of the abnormal TW. Before and after VP, atrial pacing was maintained at a stable cycle length. Simultaneous ECG was recorded before, during, and following VP to assess changes in TW polarity, amplitude, electrical axis, QTc interval, and QTc interval dispersion.

VP was followed by memory-induced changes in TW in 80% of patients in the control group. Mean T wave axis shifted from $+60^{\circ} \pm 21.2^{\circ}$ to $+23.5^{\circ} \pm 50.7^{\circ}$ ($p = 0.01$) in the frontal plane.

In the study group, complete or partial normalization of TW occurred in 17 of 18 patients. Mean T wave axis shifted from $-23.7^{\circ} \pm 22.9^{\circ}$ to $+19.7^{\circ} \pm 34.7^{\circ}$ ($p < 0.0002$) in the frontal plane when paced from RVOT. The QTc interval shortened after VP both in the control group (424 ± 25 vs. 399 ± 27 ms; $p = 0.007$) and in the study group (446 ± 26 vs. 421 ± 22 ms; $p < 0.0002$). No significant changes were found in QTc interval dispersion. The authors conclude that transient changes in the sequence of ventricular activation may either induce or normalize abnormal TW. The background of preceding ventricular depolarization needs to be taken into account before determining the clinical significance of a given pattern of ventricular repolarization.

- 1. Chiale PA, Pastori JD, Garro HA, et al. Reversal of primary and pseudo-primary T wave abnormalities by ventricular pacing. A novel manifestation of cardiac memory. J Interv Card Electrophysiol. 2010 Jun;28:23-33.**

COMPONENTS OF VENTRICULAR REPOLARIZATION THE CONTEXT OF CARDIAC MEMORY



The ventricular repolarization of ECG includes: The J point (coincident with the phase 1 of action potential), ST segment (phase 2), T wave (phase 3), and U waves (to the phase 4). On the basis of biophysical principles of ECG recording, any wave on the ECG represents a coincident voltage gradient generated by cellular electrical activity within the heart.

PHASES OF ACTION POTENTIAL

PHASE 0

Conditioned by Na^+ entrance (fast fibers) and/or Ca^{2+} (slow fibers) responsible for depolarization: QRS of surface ECG.

PHASE 1

Fast repolarization coinciding with J point, depends on Na^+ channel closure and transitory opening of the K^+ channel called I_{to} .

PHASE 2

Dome or “plateau” coinciding with the ST segment of surface ECG corresponding to slow entrance of Ca^{2+} by slow channels or $I_{\text{Ca}^{2+}\text{-L}}$.

PHASES OF ACTION POTENTIAL

PHASE 3

Coinciding with T wave of surface ECG, caused by K^+ outflow through the slow (I_{K-s}) fast (I_{K-R}) and ultra-fast channels (I_{K-UR}). In the final part of this phase additional K^+ outflow may occur through the so-called I_{K1} channel.

PHASE 4

Coinciding with the U wave of surface ECG. The Na^+/K^+ pumps act through energetic output, leaving the potential as in rest. In the initial part of this phase the i_f channel acts and in the final the $I_{Ca^{2+}-T}$ Does It.

The J and lambda waves are deflections with a dome that appears on the ECG after the QRS complex during the ST segment correspondent to phase 2 of AP. A transmural voltage gradient during initial ventricular repolarization, which results from the presence of a prominent AP notch mediated by the transient outward potassium current (I_{to}) in epicardium but not endocardium, is responsible for the registration of the J or lambda waves on the ECG. Clinical situations that are associated with J or lambda waves (the J-wave syndrome) include hypothermia, the early repolarization pattern, the Brugada syndrome and idiopathic ventricular fibrillation related to a prominent J or lambda wave in the right, inferior or inferolateral leads.

Causes of J waves I) J wave of hypothermia; II) J wave in normothermal patients: Hypercalcemia¹, injuries in the central nervous system: subarachnoid hemorrhage, post-heart arrest and in cervical sympathetic system dysfunction². early repolarization pattern³. Brugada "entities: 1) Familial cases (~17%): true Brugada disease; 2) Sporadic cases (~63%): Brugada syndrome⁴. 3) Brugada phenocopies or acquired forms: they are those clinico-pharmacological entities or circumstances, where Brugada phenotype or sign in ECG, may be found as a consequence of causing increase in I_{to} channel function in the ventricular epicardium or decrease of slow calcium channel⁵, in concealed forms of arrhythmogenic dysplasia of the right ventricle⁶; and in variant angina of Prinzmetal⁷.

- 1) Topsakal R, et al. Jpn Heart J. 2003; 44:1033-1037.
- 2) Carrillo-Esper R, et al. Cir Cir. 2004; 72:125-129.
- 3) Nava A, et al. Mises a Jour Cardiologiques 1988;17:157-159.
- 4) Schulze-Bahr E, et al. Hum Mutat. 2003;21:651-652.

The T wave marks the phase 3 of AP in ventricular repolarization and is a symbol of transmural dispersion of repolarization (TDR) in the ventricles. The electrophysiological remodeling following altered activation is characterized by distinct changes in regions proximal (early-activated) versus distal (late-activated) to the site of altered activation. The early-activated region exhibits marked attenuation of epicardial phase 1 notch due to reduced expression of the transient outward potassium current (I_{to}). This is attributed to electrotonic changes during altered activation, and angiotensin-mediated regulation of Kv4.3 (the pore-forming alpha subunit responsible for I_{to}). The late-activated region exhibits the most significant action potential (AP) prolongation due to markedly increased mechanical strain through a mechano-electrical feedback mechanism. Consequently, regionally heterogeneous AP remodeling occurs following altered activation. This enhances regional repolarization gradients that underlie the electrophysiological basis for T-wave memory.

An excessively prolonged QT interval with enhanced TDR predisposes people to develop torsade de pointes. The malignant "R-on-T" phenomenon, i.e., an premature ventricular contraction that originates on the preceding T wave, is due to transmural propagation of phase 2 reentry or phase 2 early afterdepolarization.

A pathological "U" wave as seen with hypokalemia is the consequence of electrical interaction among ventricular myocardial layers at action potential phase 4 of which repolarization slows. A physiological U wave is thought to be due to delayed repolarization of the Purkinje system.