Malattie Rare in Cardiologia: dal sintomo alla diagnosi

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Agenda

1. Malattia rara: Definizione
2. Malattie rare con manifestazioni cardiovascolari
3. Red flags clinici
4. Red flags all’ECG
5. Red flags all’imaging

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Definizione di malattia rara

- In Europa una malattia si definisce ***rara*** quando colpisce non più di 5 individui ogni 10mila persone.
- Si conoscono tra le 6mila e le 8mila malattie rare, molto diverse tra loro ma spesso con comuni problemi di ritardo nella diagnosi, mancanza di una cura, carico assistenziale.

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REVIEW ARTICLE

Classification of Rare Cardiovascular Diseases (RCD Classification), Krakow 2013

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The main classes of the RCD classification include:

- Class I – rare diseases of systemic circulation
- Class II – rare diseases of pulmonary circulation
- Class III – rare diseases of the heart (cardiomyopathies)
- Class IV – rare congenital cardiovascular diseases
- Class V – rare arrhythmias
- Class VI – cardiac tumors and cardiovascular diseases in malignancy
- Class VII – cardiovascular diseases in pregnancy
- Class VIII – unclassified rare cardiovascular diseases

Coartazione aortica, anomalie congenite delle coronarie, Sindrome di Marfan, Vasculiti (Takayasu, Kawasaki, GCA)

Ipertensione polmonare primitiva

Group	Subgroup	Examples	RCD code	ICD-10 code
Rare diseases of systemic circulation – class I				
1. Anatomical malformations of the arteries	A. Cerebral arteries	1. Anomalies of the circle of Willis	I-1A.1	Q28.3
		2. Intracerebral arteries	I-1A.2	I67.8
		3. Moyamoya disease	I-1A.3	I67.5
		– Others	I-1A.0	
	B. Aorta and aortic arch main branches	1. Right aortic arch	I-1B.1	Q25.4
		2. Double aortic arch	I-1B.2	Q25.4
		3. Aortic rings	I-1B.3	Q25
		4. Interruption of aortic arch	I-1B.4	Q25.4
		5. Variants in aortic arch arteries	I-1B.5	Q25
		6. Coarctation of the aorta	I-1B.6	Q25.1
		– Others	I-1B.0	
	C. Coronary arteries	1. Variants in the course and the number	I-1C.1	Q24.5
		2. Single coronary artery	I-1C.2	Q24.5
		3. Coronary artery originating from the pulmonary artery	I-1C.3	Q24.5
		4. Coronary fistula	I-1C.4	Q24.5
		5. Coronary artery aneurysm	I-1C.5	Q24.5
		– Others	I-1C.0	
	D. Other arteries	1. Abdominal aorta: cephalic trunk, renal, mesenteric, splenic, others	I-1D.1	Q27.2
		2. Iliac and femoral arteries	I-1D.2	Q27.8
		3. Popliteal and below the knee	I-1D.3	Q27.8
		4. Upper extremity arteries	I-1D.4	Q27.8
		– Others	I-1D.0	
2. Connective tissue disorders causing aneurysmal disease	A. Aneurysmal disease of the aorta	1. Marfan syndrome	I-2A.1	Q87.4
		2. Ehlers–Danlos syndrome	I-2A.2	I71
		3. Loeys–Dietz syndrome	I-2A.3	Q79.6
		4. Familial thoracic aortic aneurysms and dissections	I-2A.4	Q87.4
		- Others	I-2A.0	
	- Others		I-2.0	
3. Autoimmune vascular diseases	A. Primary systemic vasculitis: Predominantly large arteries	1. Takayasu's arteritis	I-3A.1	M31.4
		2. Giant-cell arteritis	I-3A.2	M31.6
		3. Isolated aortitis	I-3A.3	I77.6
		– Others	I-3A.0	
3. Autoimmune vascular diseases	A. Primary systemic vasculitis: Predominantly medium-and small-size arteries	5. Kawasaki disease	I-3A.5	M30.3
		6. Polyarteritis nodosa	I-3A.6	M30
		7. Necrotizing ANCA-associated:	I-3A.7	
		a. Churg–Strauss syndrome	I-3A.7a	M31
		b. Wegener's granulomatosis	I-3A.7b	M31.3
		c. Microscopic polyangiitis	I-3A.7c	M31.7
		d. Idiopathic necrotizing crescentic glomerulonephritis	I-3A.7d	N05.7
		8. Non-ANCA associated:	I-3A.8	
		a. Henoch–Schönlein purpura	I-3A.8a	D69
		b. Goodpasture's disease	I-3A.8b	M31.0
		c. Mixed cryoglobulinemia	I-3A.8c	D89.1
		d. Hypersensitivity vasculitis	I-3A.8d	M31.0
		– others	I-3A.8.o	
	B. Secondary systemic vasculitis	1. Secondary to infection (unknown)	I-3B.1	I77.6
		a. Viral	I-3B.1.a	
		b. Bacterial	I-3B.1.b	
		c. Fungal	I-3B.1.c	
		d. Parasitosis	I-3B.1.d	
		2. Secondary to medications	I-3B.2	
	C. Connective tissue disorders causing premature thrombosis / atherosclerosis	1. Systemic lupus erythematosus	I-3C.1	M32
		2. Scleroderma	I-3C.2	M34
		3. Antiphospholipid syndrome	I-3C.3	D68.6
		– Others	I-3C.0	
	– Others	1. Behçet's disease	I-3O.1	M35.2
		2. Cogan syndrome	I-3O.2	Q30.8
		3. Others	I-3O.0	
4. Intimal hyperplasia	A. Fibromuscular dysplasia		I-4A	I77.3
	- Others		I-4O	
5. Spontaneous dissection of the artery	A. Dissection of aortic arch arteries		I-5A	I71.0
	- Others		I-5O	
6. Premature atherosclerosis	A. Familial hypercholesterolemia		I-6A.1	E78
	B. Adult progeria – laminopathies	1. Hutchison–Gilford progeria syndrome	I-6B.1	E34.8
		2. Dunnigan-type partial lipodystrophy	I-6B.2	E88.1
		– Others	I-6B.0	
	C. Secondary	1. Polycystic ovary syndrome	I-6C.1	E28.2
		2. Acquired immunodeficiency syndrome	I-6C.2	B22.2
		– Others	I-6C.0	
– Others			I-0	

Group	Subgroup	Examples	RCD code	ICD-10 code
Rare diseases of pulmonary circulation – RCD class II				
1.Pulmonary hypertension	A. Low-prevalence pulmonary hypertension	1. Idiopathic PAH	II-1A.1	I27
		2. Heritable PAH	II-1A.2	I27
		3. Drug- and toxin-induced PAH	II-1A.3	I27.2
		4. PAH associated with:		
		a. connective tissue disease	II-1A.4a	I27.2
		b. HIV infection	II-1A.4b	I27.2
		c. portal hypertension	II-1A.4c	I27.2
		d. congenital heart diseases	II-1A.4d	I27.2
		– others	II-1A.4.o	
		5. Chronic thromboembolic pulmonary hypertension	II-1A.5	I27.2
		6. Pulmonary veno-occlusive disease	II-1A.6	I27
		7. Pulmonary hemangiomatosis	II-1A.7	D18
		8. Persistent pulmonary hypertension of the newborn	II-1A.8	P29
		– Others	II-1A.O	
	B. Severe forms of non-low-prevalence pulmonary hypertension	1. Severe pulmonary hypertension due to left heart diseases	II-1B.1	I27
		2. Severe pulmonary hypertension due to lung diseases and/or hypoxia	II-1B.2	I27.2
	C. Overlap pulmonary hypertension	1. Pulmonary hypertension in a patient with congenital shunt and left ventricular dysfunction	II-1C.1	I27
		2. Pulmonary hypertension associated with congenital heart disease complicated by thromboembolic disease	II-1C.2	I27
		– Others	II-1C.O	
2. Inborn anomalies of the pulmonary vessels	A. Anomalous morphology	1. Atresia of the pulmonary artery	II-2A.1	Q25.5
		2. Pulmonary artery coarctation	II-2A.2	Q25.7
		3. Idiopathic dilatation of the pulmonary trunk	II-2A.3	Q25
		– Others	II-2A.O	
	B. Anomalous course	1. Pulmonary artery sling	II-2B.1	Q25.6
		2. Ductal sling	II-2B.2	Q33.2
		3. Pulmonary sequestration	II-2B.3	E25.7
		– Others	II-2B.O	
	C. Anomalous connections	1. Inborn pulmonary arteriovenous fistulas	II-2C.1	Q25.7
		– Others	II-2C.O	
3. Acquired anomalies of the pulmonary vessels	A. Pulmonary vessel arteritis	1. Takayasu's arteritis	II-3A.1	M31.4
		2. Giant-cell arteritis	II-3A.2	M31.6
		3. Behçet's disease	II-3A.3	M35.2
		4. Hughes–Stovin syndrome	II-3A.4	M35.2
		5. Granulomatous vasculitis	II-3A.5	M31.3
		– Others	II-3A.O	
	B. Anomalous morphology	1. Pulmonary artery aneurysm	II-3B.1	E25.7
		– Others	II-3B.O	

Group	Subgroup	Examples	RCD code	ICD-10 code
Rare diseases of the heart (cardiomyopathies) – RCD class III				
1. Dilated cardio-myopathy	A. Genetic	1. Sarcomeric protein mutations: β-myosin heavy chain (MYH7; on chromosome 14q12), myosin-binding protein C (MYBPC3; 11p11.2), troponin T (TNNT2; 1q32), troponin C (TNNC1; 3p21.3-p14.3), α-myosin heavy chain (MYH6; 14q12), α-tropomyosin (TPM1; 15q22.1), cardiac actin (ACTC; 15q14), and titin (TTN)	III-1A.1	I42.4
		– Other		
		2. Z-band mutations	III-1A.2	I42.4
		3. Cytoskeletal gene mutations:	III-1A.3	I43
		a. Dystrophin – Duchenne muscular dystrophy	III-1A.3a	G71.0
		b. Dystrophin – Becker's muscular dystrophy	III-1A.3b	G71.0
		c. Dystrophin – Bethlem myopathy	III-1A.3c	G71.0
		d. Dystrophin – Limb-girdle muscular dystrophy	III-1A.3d	G71.0
		e. Tafazzin – Barth syndrome	III-1A.3e	E71.1
		f. Desmin mutations	III-1A.3f	G71.8
		g. Sarcoglycan complex mutations	III-1A.3g	G71.0
		– Other cytoskeletal gene mutations	III-1A.3.o	
		4. Nuclear membrane mutations:	III-1A.4	I42.4
		a. Lamins A/C – DCM + conduction disease	III-1A.4a	G71.0
		b. LaminsA/C – Emery–Dreifuss muscular dystrophy	III-1A.4b	G71.0
		– Other nuclear membrane mutations	III-1A.4.o	
		5. Mitochondrial cardiomyopathies	III-1A.5	I43
		a. Kearns–Sayre syndrome	III-1A.5a	H49.8
		– Other mitochondrial cardiomyopathies	III-1A.5.o	
	B. Nongenetic	1. Inflammatory cardiomyopathy:	III-1B.1	I42.7
		a. Viral inflammatory cardiomyopathy	III-1B.1a	B33.24
		b. Nonviral inflammatory cardiomyopathy	III-1B.1b	I42.7
		c. Autoimmune-induced inflammatory cardiomyopathy	III-1B.1c	I42.7
		– Other inflammatory cardiomyopathies	III-1B.1.o	
		2. Due to connective tissue diseases:	III-1B.2	I43
		a. Systemic lupus erythematosus	III-1B.2a	M32
		b. Scleroderma	III-1B.2b	M34
		c. Giant-cell arteritis	III-1B.2c	M31.6
		– Other due to connective tissue diseases	III-1B.2.o	
		3. Due to endocrine disorders:	III-1B.3	I43
		a. Thyroid hormone excess or deficiency	III-1B.3a	E00-07
		b. Pheochromocytoma	III-1B.3b	C75.5/D35.6
		c. Cushing's disease	III-1B.3c	E24
		– Other due to endocrine disorders	III-1B.3.o	
		4. Due to infiltrative disorders:	III-1B.4	I43
		a. Amyloidosis	III-1B.4a	E85
		b. Sarcoidosis	III-1B.4b	D86
		c. Hemochromatosis	III-1B.4c	E83.1
		– Other due to infiltrative disorders	III-1B.4.o	

Group	Subgroup	Examples	RCD code	ICD-10 code
1. Dilated cardio-myopathy	B. Nongenetic	5. Medication-induced:	III-1B.5	I42.7
		a. Anthracyclines	III-1B.5a	I42.7
		b. Cyclophosphamide	III-1B.5b	I42.7
		c. Trastuzumab	III-1B.5c	I42.7
		d. HAART-HIV: zidovudine, didanosine, zalcitabine	III-1B.5d	I42.7
		– Other	III-1B.5.o	
		6. Toxin-induced:	III-1B.6	I42.7
		a. Ethanol	III-1B.6a	I42.6
		b. Cocaine	III-1B.6b	I42.7
		c. Amphetamines	III-1B.6c	I42.7
		– Other	III-1B.6.o	
		7. Tachycardia-induced:	III-1B.7	I42.8
		a. Uncontrolled atrial fibrillation	III-1B.7a	I48
		b. Atrioventricular nodal reentry	III-1B.7b	I47.1
		c. Preexcitation syndromes	III-1B.7c	I45.6
		– Other	III-1B.7.o	
		8. End stage of other types of cardiomyopathy:	III-1B.8	I42.9
		a. Hypertrophic cardiomyopathy	III-1B.8a	I42.2
		b. Restrictive cardiomyopathy	III-1B.8b	I42.5
		c. Peripartum cardiomyopathy	III-1B.8c	O90.3
		d. Takotsubo cardiomyopathy	III-1B.8d	I51.81
		e. Left ventricular noncompaction	III-1B.8e	I42.8
		– Other	III-1B.8.o	
		9. Miscellaneous:	III-1B.9	I43
		a. Neoplastic heart disease	III-1B.9a	D15.1
		b. Celiac disease	III-1B.9b	K90
		c. Extensive chest radiation	III-1B.9c	Y84.2
		d. Nutritional (thiamine, selenium, L-carnitine)	III-1B.9d	I43.2
		e. Obstructive sleep apnea	III-1B.9e	G47.3
		– Other	III-1B.9.o	
2.Hypertrophic cardiomyopathy	A. Sarcomeric protein mutations	1. MYH7, MYBPC3, TNNT2, MYH6, TPM1, TNNC1, ACTC, TTN	III-2A.1	I42.2
	B.Nonsarcomeric protein mutations	1. Glycogen storage disease:	III-2B.1	I43.1
		a. Pompe disease	III-2B.1a	E74.0
		b. Danon disease	III-2B.1b	E74.0
		c. Forbes disease	III-2B.1c	E74.0
		– Other	III-2B.1.o	
		2. Lysosomal storage disease:	III-2B.2	I43.1
		a. Fabry disease	III-2B.2a	E75.2
		b. Hurler syndrome	III-2B.2b	E76
		c. Hunter syndrome	III-2B.2c	E76.1
		d. Maroteaux–Lamy disease	III-2B.2d	E76.2
		e. Gangliosidosis	III-2B.2e	E75.1
		f. Gaucher's diseases	III-2B.2f	E75.2
		g. Niemann–Pick disease	III-2B.2g	E75.2
		– Other	III-2B.2.o	
		3. Metabolic myopathies:	III-2B.3	I43.1
		a. Disorders of fatty metabolism	III-2B.3a	E78
		b. Carnitine deficiency	III-2B.3b	E71.3
		c. Phosphorylase-b kinase deficiency	III-2B.3c	E74
		– Other	III-2B.3.o	
		4. Systemic diseases:	III-2B.4	I43
		a. Pheochromocytoma	III-2B.4a	C75.5/D35.6
		b. Neurofibromatosis	III-2B.4b	Q85.0
		c. Tuberous sclerosis	III-2B.4c	Q85.1
		– Other	III-2B.4.o	
		5. Mitochondrial cardiomyopathies	III-2B.5	I43
2. Hypertrophic cardiomyopathy	B. Nonsarcomeric protein mutations	6. Syndromic HCM:	III-2B.6	I43
		a. Noonan syndrome	III-2B.6a	Q87.1
		b. LEOPARD syndrome	III-2B.6b	Q87.8
		c. Friedreich's ataxia	III-2B.6c	G11.1
		d. Swyer syndrome	III-2B.6d	Q97.3
		e. Costello syndrome	III-2B.6e	Q87.8
		– Other	III-2B.6.o	
3. Restrictive cardiomyopathy	A. Infiltrative	1. Familial amyloidosis	III-3A.1	E85
		a. Transthyretin	III-3A.1a	E85.1
		b. Apolipoprotein	III-3A.1b	E85
		2. Amyloid	III-3A.2	E85.1
		a. AL (prealbumin	III-3A.2a	E85.1
		3. Sarcoidosis	III-3A.3	D86
		4. Gaucher's disease	III-3A.4	E75.2
		5. Hurler syndrome	III-3A.5	E76
		6. Fatty infiltration	III-3A.6	E78
		– Other	III-3A.O	
	B. Storage	1. Hemochromatosis	III-3B.1	E83.1
		2. Fabry disease	III-3B.2	E75.2
		3. Glycogen storage disease	III-3B.3	E74
		– Other	III-3B.O	
	C. Noninfiltrative	1. Scleroderma	III-3C.1	M34
		2. Pseudoxanthoma elasticum	III-3C.2	Q82.8
		– Other	III-3C.O	
	D. Sarcomeric protein mutations	Troponin I, essential light chain of myosin	III-3D	I43
	E. Desminopathy		III-3E	G71.8
	F. Endocardial pathology	1. Endomyocardial fibrosis with hypereosinophilia:	III-3F.1	I42.3
		a. Parasitic infection	III-3F.1a	
		b. Drugs – methysergide	III-3F.1b	
		c. Persistent inflammation	III-3F.1c	
		d. Nutritional factors	III-3F.1d	
		2. Endomyocardial disease without hypereosinophilia	III-3F.2	I42.3
		– Other	III-3F.O	
4. Arrhythmogenic right ventricular cardiomyopathy	A. Desmosomal ARVC	1. Autosomal dominant inheritance pattern:	III-4A	I42.8
		a. ARVD8 – Desmoplakin mutations	III-4A.1a	
		b. ARVD9 – Plakophilin-2 mutations	III-4A.1b	
		– Other	III-4A.1.o	
		2. Syndromic ARVC (autosomal recessive)	III-4A.2	I42.8
		a. Naxos disease – Plakoglobin mutations	III-4A.2a	Q87.8
		b. Carvajal syndrome – Desmoplakin mutations	III-4A.2b	I42
		c. Alcalai syndrome	III-4A.2c	I42
		– Other	III-4A.2.o	
	B. Nondesmosomal ARVC	1. ARVD1 – Transforming growth factor mutations	III-4B.1	I42.8
		2. ARVD2 – Cardiac ryanodine receptor mutations	III-4B.2	
		– Other	III-4B.O	

Group	Subgroup	Examples	RCD code	ICD-10 code
5. Unclassified cardiomyopathies	A. Left ventricular noncompaction	1. Genetic causes of LVNC:	III-5A.1	I42.9
		a. Tafazzin mutations	III-5A.1a	
		b. Dystrobrevin mutations	III-5A.1b	
		– Other	III-5A.1.o	
		2. Metabolic disorders/genetic syndromes and LVNC	III-5A.2	I42.9
		a. Barth syndrome	III-5A.2a	E71.1
		b. Beals syndrome	III-5A.2b	Q87.8
		c. Becker's muscular dystrophy	III-5A.2c	G71
		d. Charcot–Marie–Tooth disease	III-5A.2d	G60
		e. Duchenne muscular dystrophy	III-5A.2e	G71
		f. Melnick-needles syndrome	III-5A.2f	Q77.8
		g. Myotonic dystrophy	III-5A.2g	G71.1
		h. Myoadenylate deaminase deficiency	III-5A.2h	E79.8
		i. Nail-patella syndrome	III-5A.2i	Q87.2
		j. Noonan syndrome	III-5A.2j	Q87.1
		k. Roifman syndrome	III-5A.2k	D81.8
		l. Trisomy 13	III-5A.2l	Q90
		– Other	III-5A.2.o	
	B. Takotsubo cardiomyopathy		III-5B	I42.8
	C. Peripartum cardiomyopathy		III-5C	O90.3

Rare congenital cardiovascular diseases – RCD class IV				
1. Abnormalities of the position and connection of the heart and vessels	A. Heart position	1. Dextrocardia	IV-1A.1	Q24.0
		2. Mesocardia	IV-1A.2	Q24.8
		3. Dextroposition	IV-1A.3	Q20.3
		4. Ectopia cordis	IV-1A.4	Q24.8
		– Others	IV-1A.O	
	B. Heart chambers	1. Atria	IV-1B.1	
		a. Cor triatriatum	IV-1B.1a	Q24.2
		– others	IV-1B.1.o	
		2. Ventricles	IV-1B.2	
		a. Congenitally corrected transposition of the great artery	IV-1B.2a	Q20.5
		– others	IV-1B.2o	
	C. Veins and arteries	1. Systemic veins	IV-1C.1	
		a. Left superior vena cava	IV-1C.1a	Q26.1
		– others	IV-1C.1.o	
		2. Pulmonary veins	IV-1C.2	
		a. Pulmonary vein stenosis	IV-1C.2a	Q26.2
		– others	IV-1C.2.o	
		3. Great arteries	IV-1C.3	
		a. Transposition of the great arteries	IV-1C.3a	Q20.3
		b. Truncus arteriosus	IV-1C.3b	
		– others	IV-1C.3.o	Q20.0
	D-Valves	1. Right heart valves	IV-1D.1	
		a. tricuspid atresia	IV-1D.1a	Q22.4
		b. Ebstein's anomaly	IV-1D.1b	Q22.5
		c. pulmonary valve atresia	IV-1D.1c	Q22.0
		d. pulmonary valve stenosis	IV-1D.1d	Q22.1
		– others	IV-1D.1o	

Cardiomyopathy

A myocardial disorder in which the heart muscle is structurally and functionally abnormal, in the absence of coronary artery disease, hypertension, valvular disease and congenital heart disease sufficient to cause the observed myocardial abnormality.

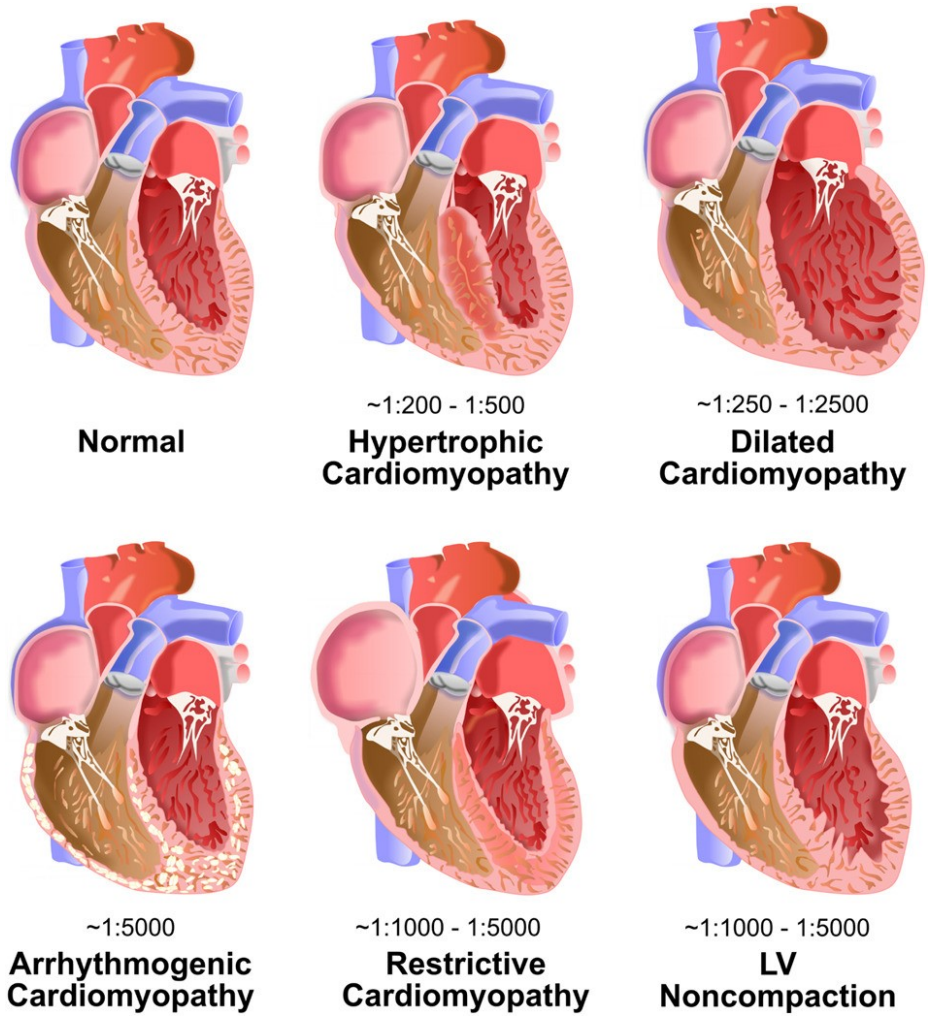
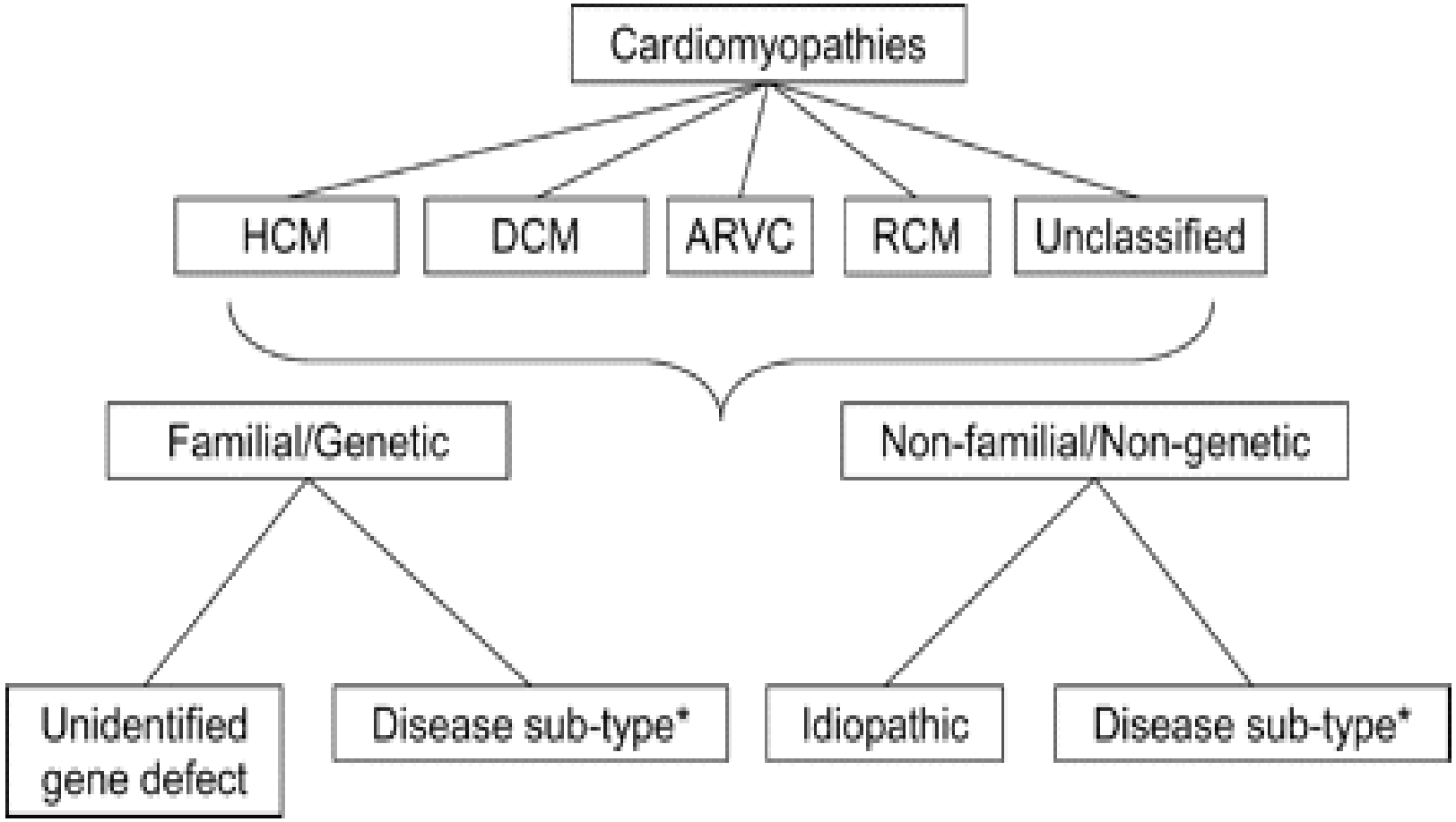


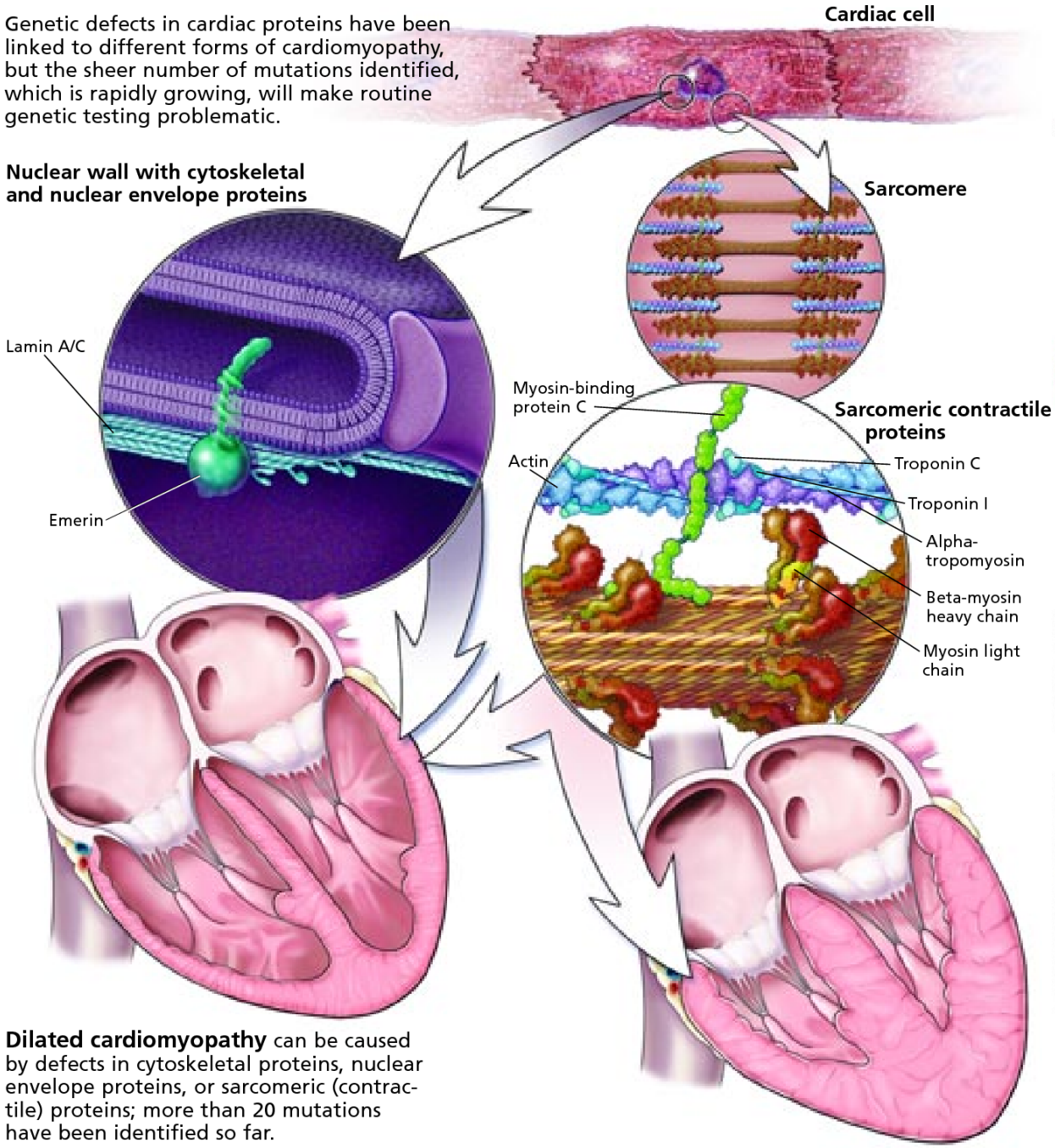
Figure 1 Summary of proposed classification system. ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, ...



Eur Heart J, Volume 29, Issue 2, January 2008, Pages 270–276, https://doi.org/10.1093/eurheartj/ehm342

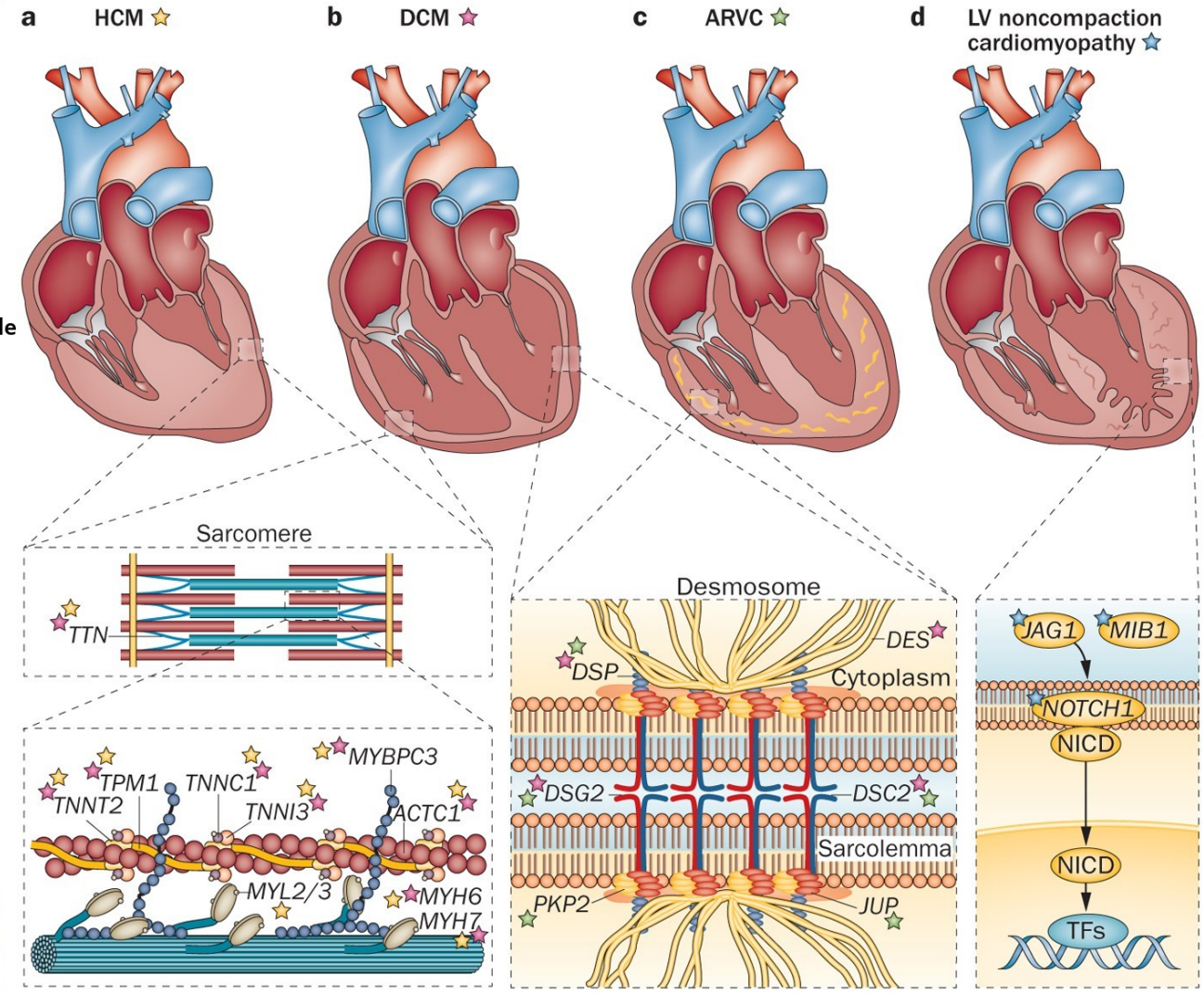
The molecular basis of cardiomyopathy

Genetic defects in cardiac proteins have been linked to different forms of cardiomyopathy, but the sheer number of mutations identified, which is rapidly growing, will make routine genetic testing problematic.



Dilated cardiomyopathy can be caused by defects in cytoskeletal proteins, nuclear envelope proteins, or sarcomeric (contractile) proteins; more than 20 mutations have been identified so far.

Hypertrophic cardiomyopathy is caused by



Group	Subgroup	Examples	RCD code	ICD-10 code
1. Abnormalities of the position and connection of the heart and vessels	D-Valves	2. Left heart valves	IV-1D.2	
		a. mitral stenosis	IV-1D.2a	Q23.2
		b. mitral subvalvular apparatus abnormalities	IV-1D.2b	Q23.8
		c. aortic stenosis	IV-1D.2c	Q23.0
		d. aortic regurgitation,	IV-1D.2d	Q23.1
		– others	IV-1D.2o	
2. Shunts	A. Decreased pulmonary flow	1. Tetralogy of Fallot	IV-2A.1	Q21.3
		2. Pulmonary stenosis and ventricular septal defect	IV-2A.2	Q21.3
		3. Pulmonary atresia and ventricular septal defect	IV-2A.3	Q25.5
		– Others	IV-2A.O	
	B. Increased pulmonary flow	1. Atrial septum	IV-2B.1	Q21.1
		2. Atrioventricular junction	IV-2B.2	Q21.2
		3. Ventricular septum	IV-2B.3	Q21.0
		4. Aortopulmonary communication	IV-2B.4	Q21.4
		– Others	IV-2B.O	
3. Complex congenital cardiovascular diseases	A. Complex abnormalities of the position and connection of the heart and vessels		IV-3A	Q20
	B. Complex abnormalities of position and connection of the heart and vessels with shunts		IV-3B	Q20
	– Others		IV-3.O	
4. Congenital cardiovascular diseases with concomitant organ dysfunction	A. Nervous system		IV-4A	G00-99
	B. Pulmonary system		IV-4B	J00-99
	C. Endocrine system		IV-4C	E00-90
	D. Thrombosis and hemostasis disorders		IV-4D	D65-69
	– Others		IV-4.O	
5. Grown-up congenital cardiovascular diseases	A. After correction	1. No complication without residual defects	IV-5A.1	Z92.4
		2. Postprocedural complication and residual defects	IV-5A.2	Z92.4
		– Others	IV-5A.O	
	B. After palliative procedures	1. Fontan procedure	IV-5B.1	Z92.4
		2. Systemic-pulmonary anastomosis	IV-5B.2	Z92.4
		– Others	IV-5B.O	
	C. Uncorrectable		IV-5C	
6. Others		1. Double-chambered left ventricle	IV-6.1	Q20
		– Others	IV-6.O	

Group	Subgroup	Examples	RCD code	ICD-10 code
Rare arrhythmias – RCD class V				
1. Arrhythmias due to primary electrical diseases of the heart	A. Channellopathies	1. Brugada syndrome	V-1A.1	I47.2
		2. Long QT syndrome (LQTS)	V-1A.2	I45.8
		3. Short QT syndrome (SQTS)	V-1A.3	I45.8
		4. Catecholaminergic polymorphic ventricular tachycardia	V-1A.4	I45.8
		– Others	V-1A.O	
	B. Preexcitation syndromes	1. Wolff–Parkinson–White syndrome	V-1B.1	I45.6
		2. Mahaim syndrome	V-1B.2	I45.6
		– Others	V-1B.O	
	– Others		V-10	
2. Arrhythmias secondary to rare structural diseases of the heart	A. In the course of cardiomyopathies	1. Arrhythmogenic right ventricular dysplasia/ cardiomyopathy	V-2A.1	I42.8
		2. Hypertrophic cardiomyopathy	V-2A.2	I42
		3. Restrictive cardiomyopathy	V-2A.3	I42
		4. Left ventricular noncompacted cardiomyopathy	V-2A.4	I42.8
		5. Dilated cardiomyopathy	V-2A.5	I42
		– Others	V-2A.O	
	B. Due to congenital heart diseases	1. Univentricular heart	V-2B.1	Q20.4
		2. Shunts	V-2B.2	
		3. Cor triatriatum	V-2B.3	Q24.2
		4. Persistent left superior vena cava	V-2B.4	Q26.1
		– Others	V-2B.O	
3. Arrhythmias of atypical mechanism and ECG presentation	A. Supraventricular	1. Atypical atrioventricular nodal recurrent tachycardia (AVNRT)	V-3A.1	I47.1
		2. Tachycardia with RP interval longer than PR	V-3A.2	I.47.1
		3. Antidromic atrioventricular tachycardia in Wolff–Parkinson–White syndrome	V-3A.3	I45.6
		4. Tachycardia in Mahaim syndrome	V-3A.4	I.47.1
		– Others	V-3A.O	
	B. Ventricular	1. Bundle branch reentry tachycardia	V-3B.1	I.47.2
		– Others	V-3B.O	
	– Others		V-30	
4. Arrhythmias in rare and specific clinical settings	A. Iatrogenic	1. Cardiotoxicity of chemotherapy	V-4A.1	Z51.1
		2. Post heart transplantation	V-4A.2	Z94.1
		3. Postsurgical correction of congenital heart diseases	V-4A.3	Y83
		- Others	V-4A.0	
	B. Metabolic disorders	1. Fabry disease	V-4B.1	E75.2
		2. Niemann–Pick disease	V-4B.2	E75.2
		– Others	V-4B.O	
	– Others		V-40	

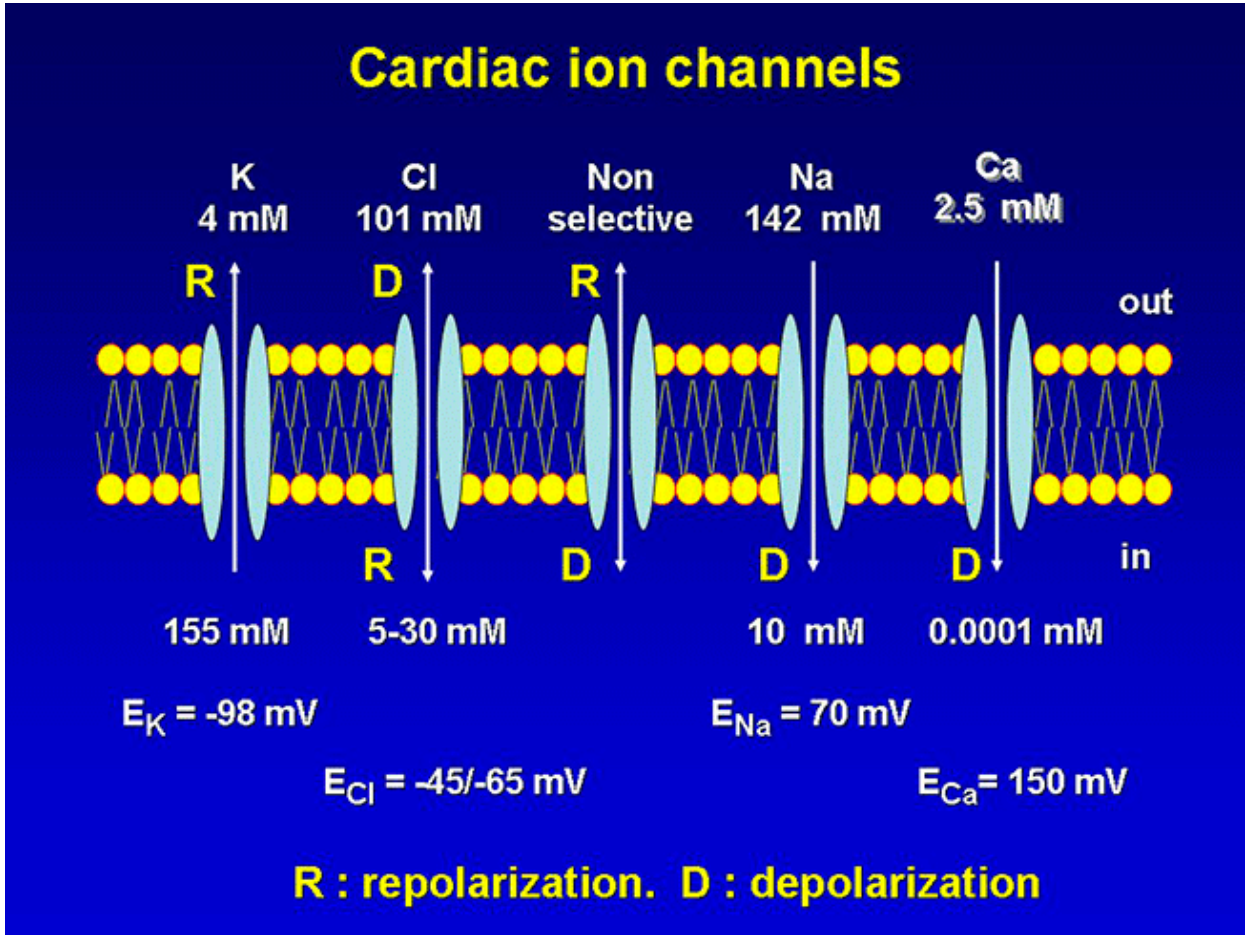
Channelopathies

Definition: A disease caused by mutations of ion channels.

Increasingly recognized as important cause of disease (>30 diseases).

Numerous mutation sites may cause similar channelopathy e.g. cystic fibrosis where

>1000 different mutations of CFTR described



Canalopatie e Cardiomiopatie

Canalopatie

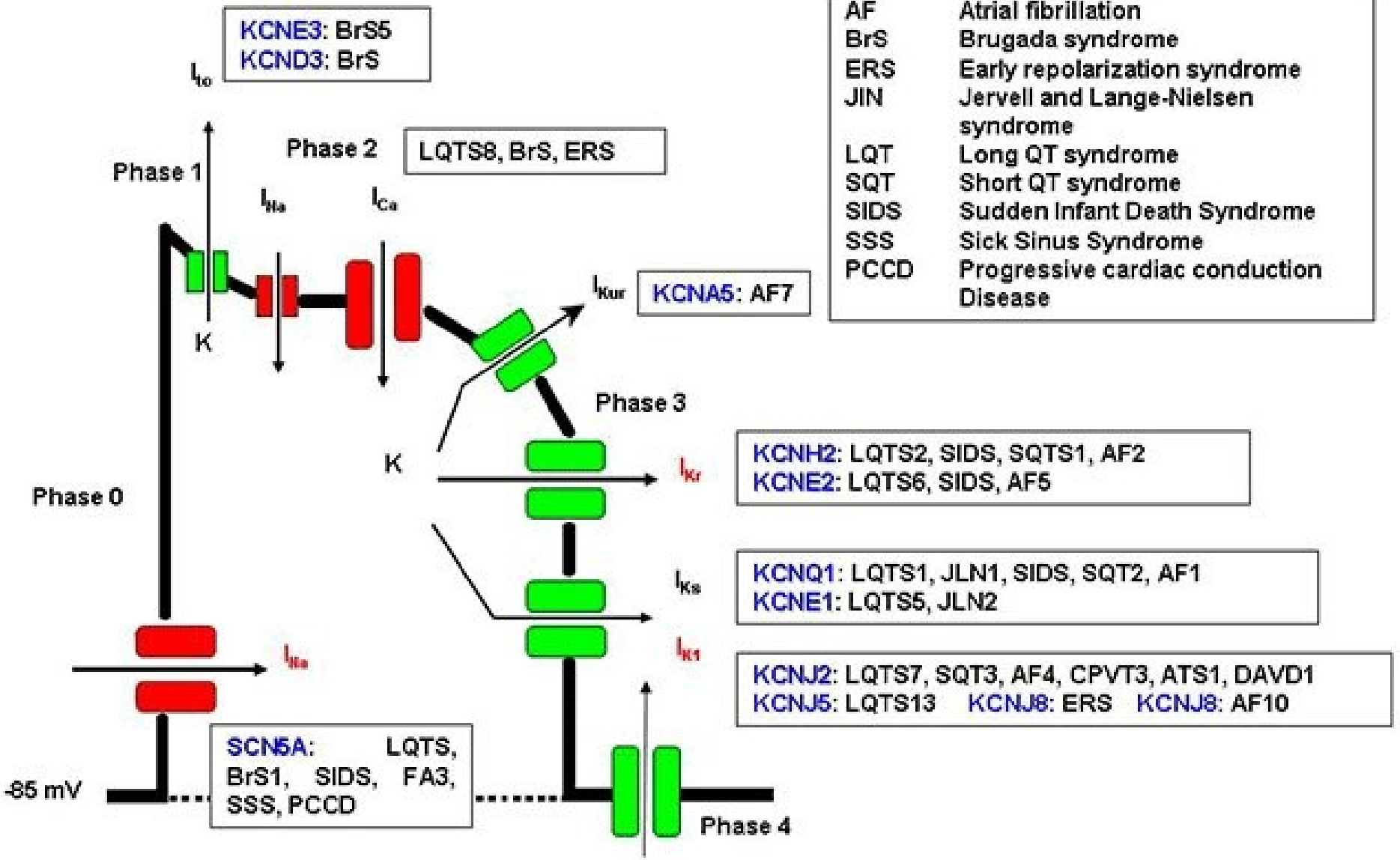
- **Sindrome del QT lungo** (LQT)
- **Sindrome di Brugada** (BrS)
- **Tachicardia Catecolaminergica Polimorfa** (CPVT)
- **Sindrome del QT corto** (SQT)

Cardiomiopatie

- **Cardiomiopatia aritmogena del ventricolo destro** (ARVC)
- **Cardiomiopatia Ipertrofica** (HCM)
- **Cardiomiopatia Dilatativa** (DCM)

Patologie genetiche

Cardiac channelopathies



AF	Atrial fibrillation
BrS	Brugada syndrome
ERS	Early repolarization syndrome
JIN	Jervell and Lange-Nielsen syndrome
LQT	Long QT syndrome
SQT	Short QT syndrome
SIDS	Sudden Infant Death Syndrome
SSS	Sick Sinus Syndrome
PCCD	Progressive cardiac conduction Disease

Group	Subgroup	Examples	RCD code	ICD-10 code
Cardiac tumors and cardiovascular diseases in malignancy – RCD class VI				
1. Primary cardiac tumors	A. Primary benign tumors	1. Myxoma	VI-1A.1	D15.1
		2. Fibroma	VI-1A.2	D15.1
		3. Lipoma a. Lipomatous hypertrophy – others	VI-1A.3 VI-1A.3a VI-1A.3.o	D17.0
		4. Rhabdomyoma	VI-1A.4	D21.3
		– Others	VI-1A.O	
	B. Primary malignant tumors	1. Rhabdomyosarcoma	VI-1B.1	C49.3
		2. Angiosarcoma	VI-1B.2	D38.0
		3. Lymphoma	VI-1B.3	C85.9
		4. Hemangioma	VI-1B.4	D18
		– Others	VI-1B.O	
2. Metastatic cardiac tumors	A. Thorax	1. Lung cancer	VI-2A.1	C34.8
		2. Breast cancer	VI-2A.2	C50.8
		– Others	VI-2A.O	
	B. Abdomen	1. Gastrointestinal tract cancer	VI-2B.1	C26.8
		2. Urinary tract and kidney cancer	VI-2B.2	C68.8
		3. Prostate cancer	VI-2B.3	C61
		4. Reproductive system cancer	VI-2B.4	C57.0
		– Others	VI-2B.O	
	C. Hematological system	1. Leukemia	VI-2C.1	C81-96
		2. Lymphoma	VI-2C.2	C81-96
		– Others	VI-2C.O	
	D. Skin cancer		VI-2D	C44
	– Others		VI-2O	
3. Thrombus within heart chambers			VI-3	I74.0
4. Inflammatory malformations	A. Vegetations		VI-4A	I80.9
	B. Inflammatory tumors		VI-4B	R22.6
	C. Abscesses		VI-4C	J85.3
	D. Calcifications	1. Pericardium	VI-4D.1	I32
		2. Valves	VI-4D.2	I39
		– Others	VI-4D.O	
	– Others		VI-4O	
5. Cardiovascular complications of oncological therapy	A. Post-surgery		VI-5A	Y83
	B. Post-radiotherapy		VI-5B	Y84.2
	C. Post-chemotherapy		VI-5C	Z51.1
	– Others		VI-5O	

Cardiovascular diseases in pregnancy – class VII*

rare cardiovascular diseases – main classes (table 1–6)	Following characters for subgroups, examples, according to the tables I–VI and VIII			CRCD code	ICD 10
	Group	Subgroup	Example		
rare diseases of systemic circulation (class I)	1…	A…	1…	VII-I-…	O99.4
rare diseases of pulmonary circulation (class II)	1…	A…	1…	VII-II-…	O99.4
rare diseases of the heart (cardiomyopathies) (class III)	1…	A…	1…	VII-III…	O99.4
rare congenital cardiovascular diseases (class IV)	1…	A…	1…	VII-IV…	O99.4
rare arrhythmias (class V)	1…	A…	1…	VII-V…	O99.4
cardiac tumors and cardiovascular diseases in malignancy (class VI)	1…	A…	1…	VII-VI…	O99.4
Unclassified rare cardiovascular diseases (class VIII)	1…	A…	1…	VII-VIII…	

* The digit VII at the front, indicates class VII and is followed by an appropriate RCD classification code corresponding to a rare cardiovascular entity found in class I to VI. Example: VII-I-1A.1 indicates a pregnant woman with anomaly of the circle of Willis, an entity included in class I of the RCD classification: Class VII – rare cardiovascular diseases in pregnancy, class I – rare diseases of the systemic circulation, group 1 – anatomical malformations of the arteries, subgroup A – cerebral arteries, example 2 – anomalies of the circle of Willis

Agenda

1. Malattia rara: Definizione
2. Malattie rare con manifestazioni cardiovascolari
3. Red flags clinici
4. Red flags all'ECG
5. Red flags all'imaging

Red flags nelle malattie rare CV

'Red fiags' are **alarm or warning symptoms, signs and near- patient diagnostic tests that suggest a potentially serious underlying disease**. All red fiags can be regarded as 'diagnostic tests', in that their presence or absence adjusts the probability of a serious diagnosis.

Red flags nelle malattie rare CV

- Anamnesi: storia clinica di affezioni associate, familiarità
- Segni o sintomi
- Esami di laboratorio alterati
- Alterazione ECG
- Reperto di imaging (ECO, RM cardiaca)

European Heart Journal (2013) **34**, 1448–1458
doi:10.1093/eurheartj/ehs397

SPECIAL ARTICLE

Diagnostic work-up in cardiomyopathies: bridging the gap between clinical phenotypes and final diagnosis. A position statement from the ESC Working Group on Myocardial and Pericardial Diseases

Claudio Rapezzi, Eloisa Arbustini, Alida L. P. Caforio, Philippe Charron, Juan Gimeno-Blanes, Tiina Heliö, Ales Linhart, Jens Mogensen, Yigal Pinto, Arsen Ristic, Hubert Seggewiss, Gianfranco Sinagra, Luigi Tavazzi, and Perry M. Elliott*

RED FLAGS IN CARDIOLOGIA: Segni e Sintomi

Table 2 **Examples of signs and symptoms that should raise the suspicion of specific diagnoses grouped according to the main echocardiographic phenotype**

Finding	Main echocardiographic phenotype			
	HCM	DCM	ARVC	RCM
Learning difficulties, mental retardation	Mitochondrial diseases Noonan syndrome Danon disease	Dystrophinopathies Mitochondrial diseases Myotonic dystrophy *FKTN* mutations		Noonan syndrome
Sensorineural deafness	Mitochondrial diseases Anderson–Fabry disease LEOPARD syndrome	Epicardin mutation Mitochondrial diseases		
Visual impairment	Mitochondrial diseases (retinal disease, optic nerve) TTR-related amyloidosis (vitreous opacities, cotton wool type) Danon disease (retinitis pigmentosa) Anderson–Fabry disease (cataracts, corneal opacities)	*CRYAB* (polar cataract) *Type 2 myotonic dystrophy* (subcapsular cataract)		
Gait disturbance	Friedreich's ataxia	Dystrophinopathies Sarcoglycanopathies Myofibrillar myopathies		
Myotonia (involuntary muscle contraction with delayed relaxation)		Myotonic dystrophy (type 1 and type 2)		
Paraesthesiae/sensory abnormalities/neuropathic pain	Amyloidosis Anderson–Fabry disease			Amyloidosis
Carpal tunnel syndrome (bilateral)	TTR-related amyloidosis			Amyloidosis
Muscle weakness	Mitochondrial diseases Glycogenosis *FHL1* mutation	Dystrophinopathies Sarcoglycanopathies Laminopathies Myotonic dystrophy Desminopathy		Desminopathies (generally distal progressing to proximal)
Palpebral ptosis	Mitochondrial diseases Myotonic dystrophy			
Lentigines/café au lait spots	LEOPARD syndrome			
Angiokeratomata Hypohidrosis	Anderson–Fabry disease			
Pigmentation of skin and scars		Haemochromatosis		
Palmoplantar keratoderma and woolly hair		Carvajal syndrome	Naxos and Carvajal syndromes	

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; TTR, transthyretin.

Agenda

1. Malattia rara: Definizione
2. Malattie rare con manifestazioni cardiovascolari
3. Red flags clinici
4. Red flags all’ECG
5. Red flags all’imaging

CHE COS'È L'ELETTROCARDIOGRAMMA?

L'elettrocardiogramma (ECG) è la registrazione dell'attività elettrica del cuore.
L'ECG non dà informazioni sulla attività meccanica cardiaca!
L'elettrocardiogramma standard è costituito da 12 derivazioni.

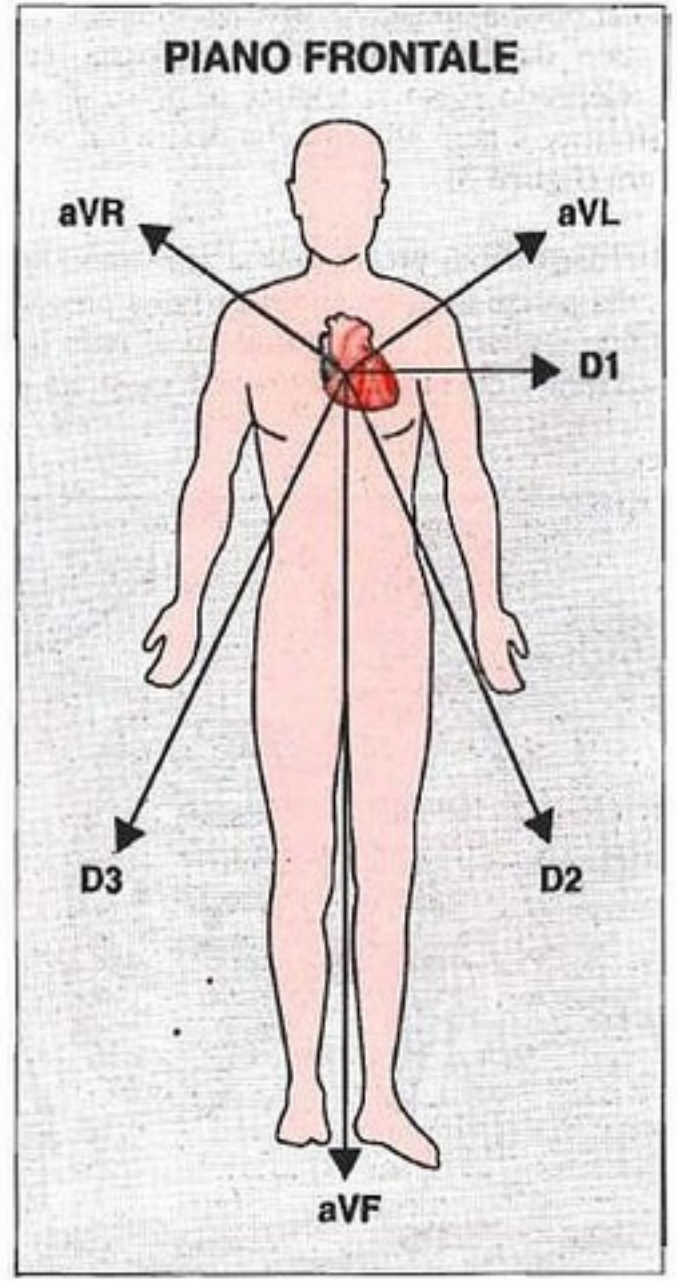
CHE COSA SONO LE DERIVAZIONI?

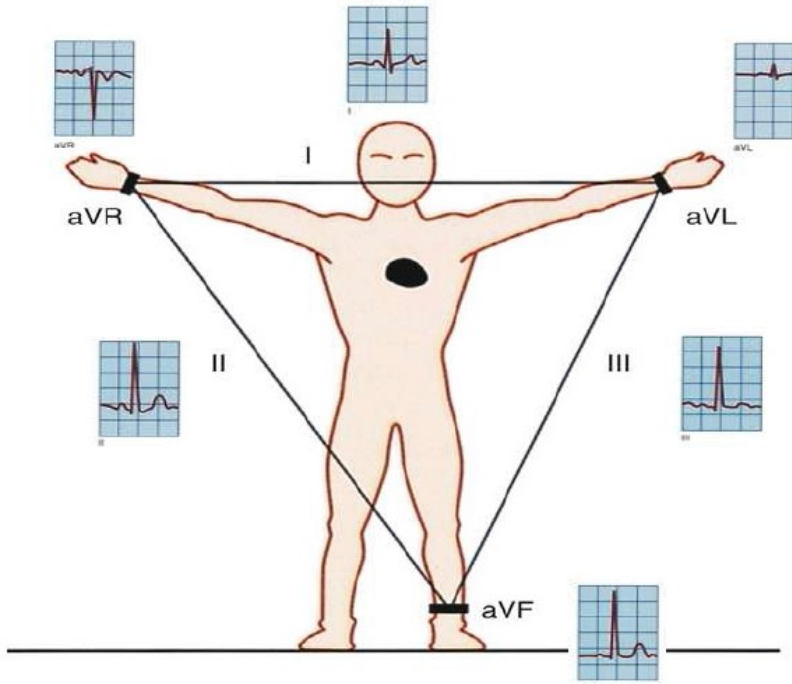
Le derivazioni ECG sono posizioni da cui si osserva l'attivazione elettrica degli atrii e dei ventricoli:

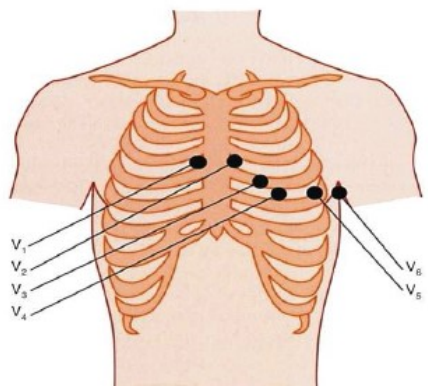
- Le derivazioni periferiche sono:
  D1, D2, D3, aVR, aVL, aVF.

- Le derivazioni precordiali sono:
  V1, V2, V3, V4, V5, V6.

Le derivazioni periferiche esplorano l'attività elettrica sul piano frontale
Le derivazioni precordiali esplorano l'attività elettrica sul piano orizzontale







ECG comprende 12 registrazioni

6 dagli arti:

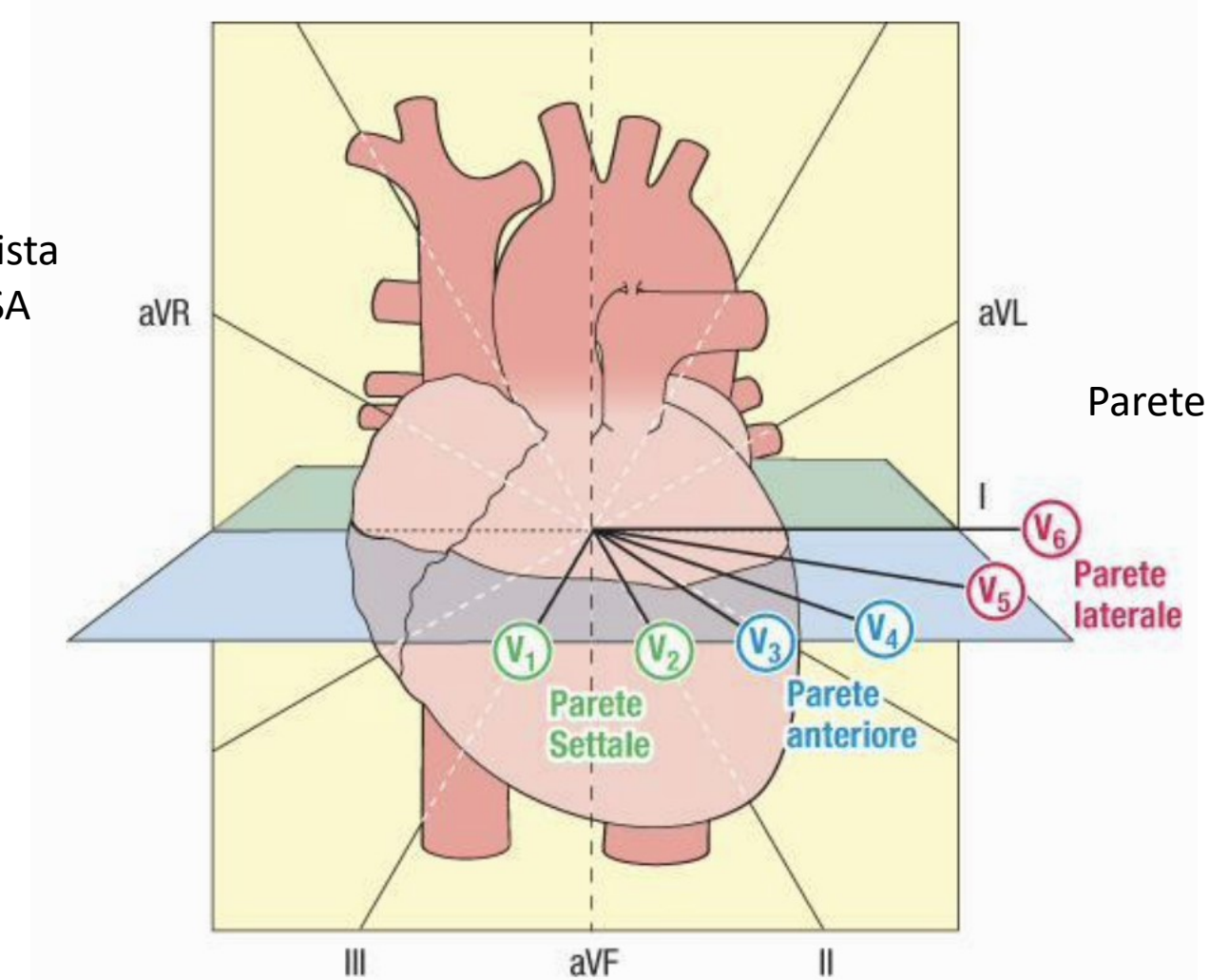
3 bipolari (I, II, III)

3 unipolari (aVR, aVL, aVF)

6 dal torace:

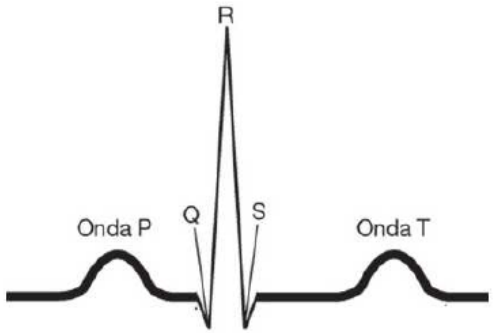
Unipolari toraciche o precordiali (V1-V6)

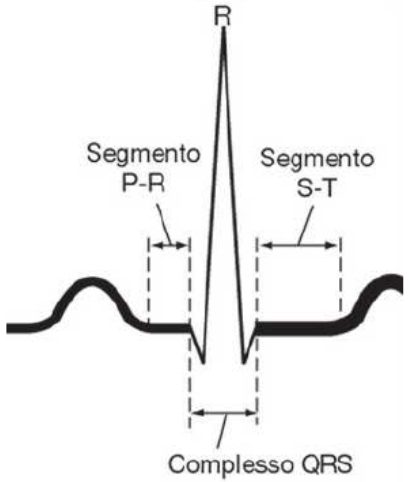
Punto di vista
del nodo SA

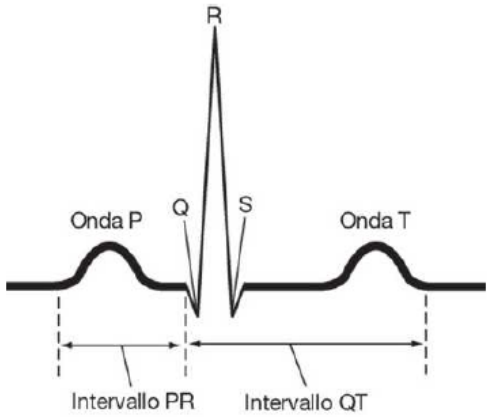


Parete Laterale

Parete Inferiore







ONDE

- **Onda P**: Depolarizzazione atri
- **Complesso QRS**: Depolarizzazione ventricoli: setto, apice, base
- **Onda T**: Ripolarizzazione ventricoli

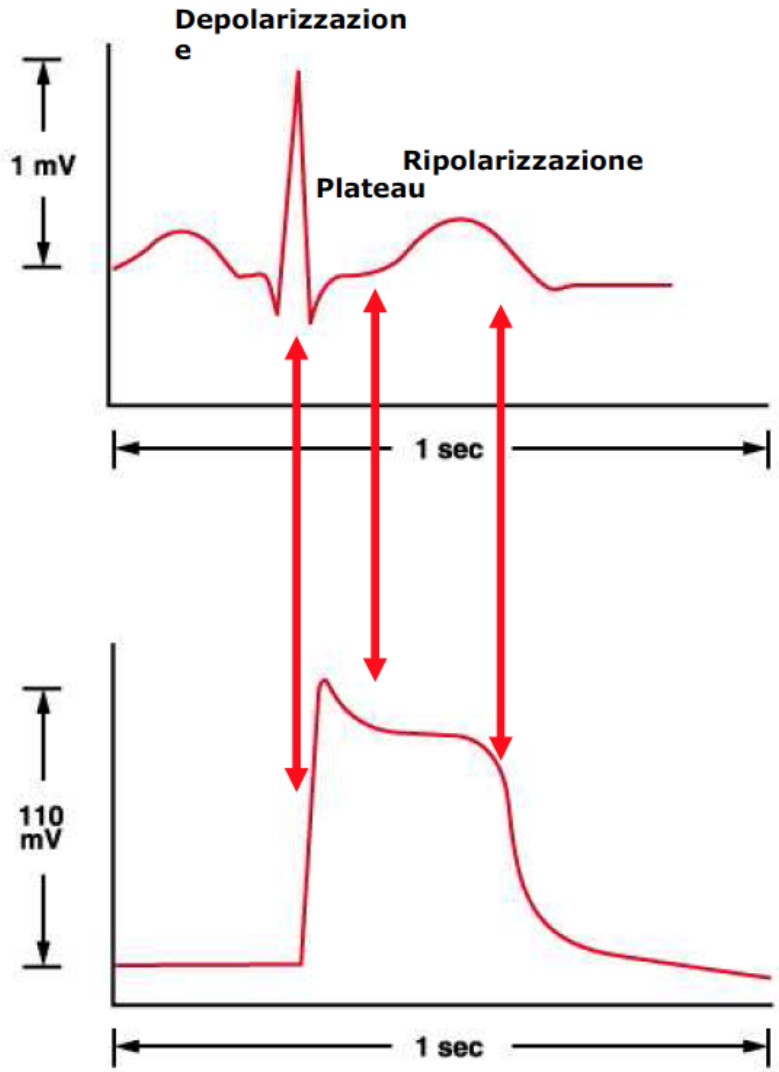
Non è visibile, nell'ECG un'onda di ripolarizzazione degli atri, perché la contemporanea depolarizzazione ventricolare, maschera le variazioni di potenziale relative a quest'evento.

SEGMENTI-TRATTI

- **Segmento P-R**: (fine onda P - inizio complesso QRS). Gli atri sono totalmente depolarizzati
- **Segmento S-T**: (fine onda S - inizio onda T). I ventricoli sono totalmente depolarizzati

INTERVALLI

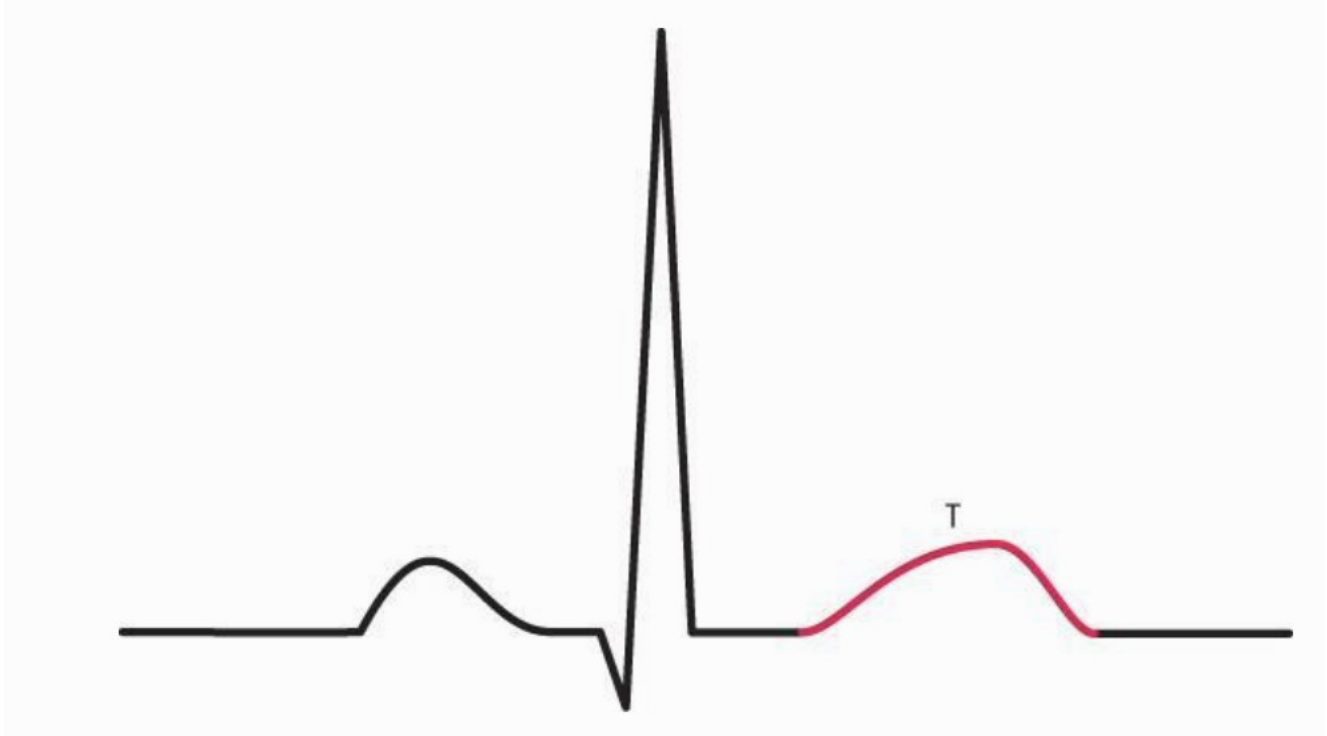
- **Intervallo P-R**: Tempo conduzione atrio-ventricolare
- **Intervallo Q-T**: Tempo depolarizzazione-ripolarizzazione ventricolare



Variazioni di potenziale misurate extracellularmente durante le diverse fasi dell'eccitamento ventricolare

Corrispondenti fasi dell'eccitamento, registrate intracellularmente

Di Grassi S.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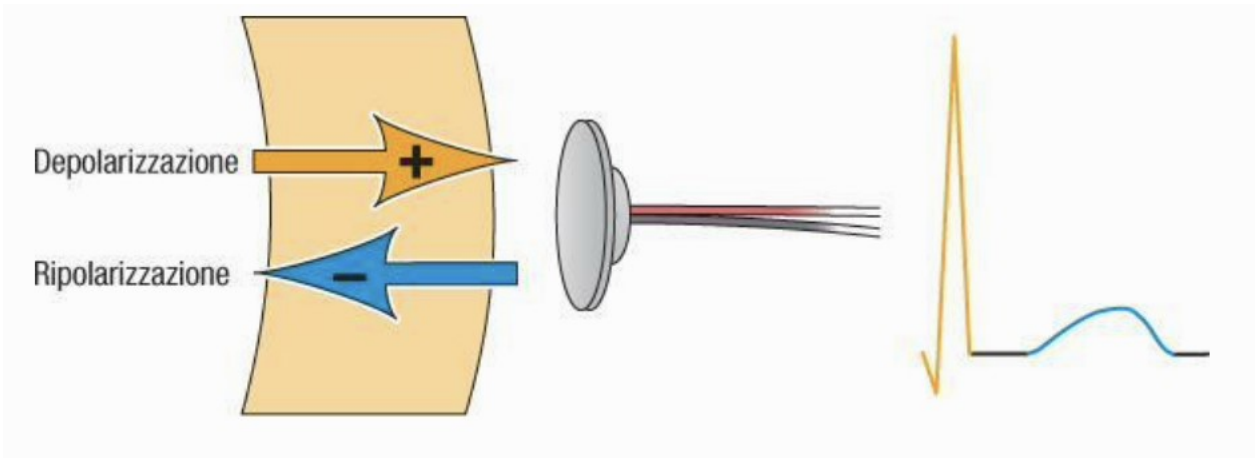

Depolarizzazione
+
Ripolarizzazione
−

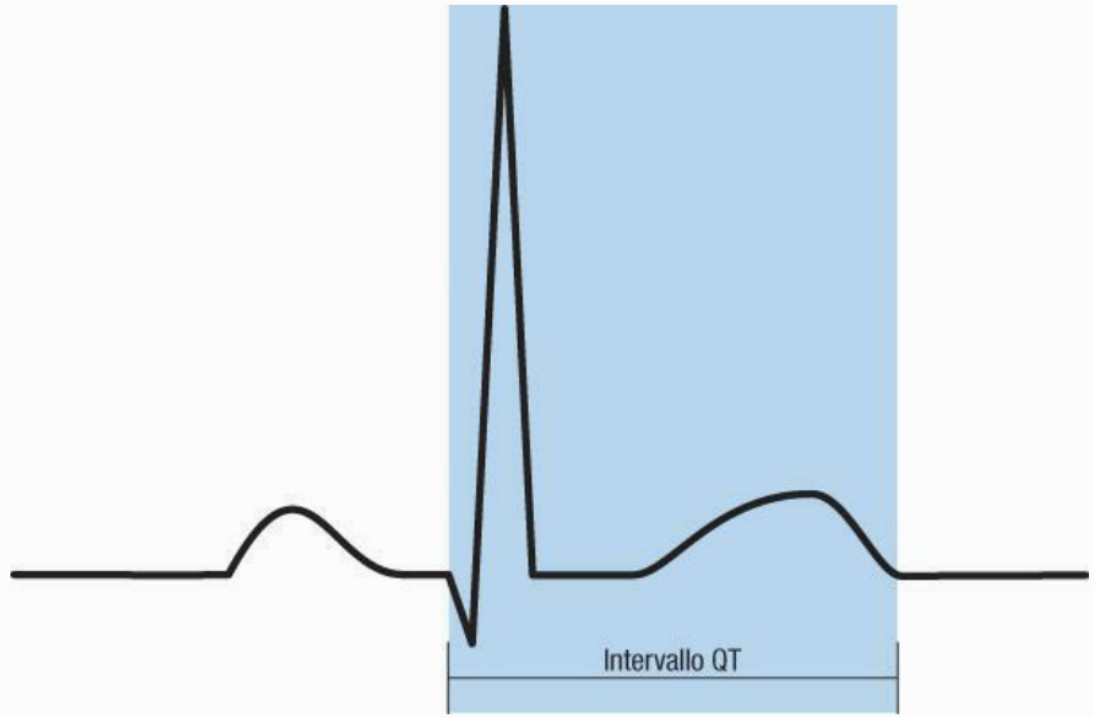


Figura 6-17 L'intervallo QT.

RICORDA

Eventi cardiaci rappresentati dall'intervallo QT: tutti gli eventi della sistole ventricolare

Durata normale: variabile, specialmente in base alla frequenza. Solitamente inferiore alla metà dell'intervallo RR

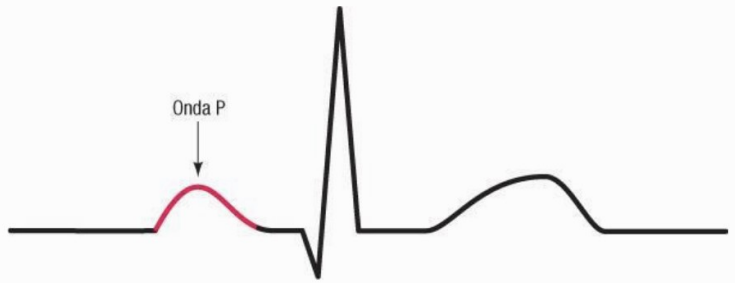


Figura 9-1 L'onda P.

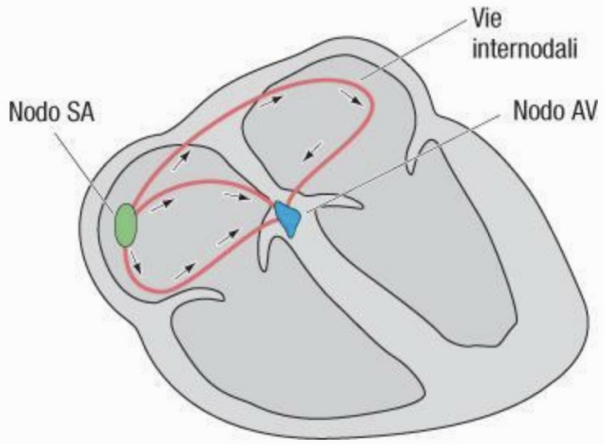


Figura 9-2 Trasmissione dell'onda P dal nodo seno-atriale al nodo atrio-ventricolare.

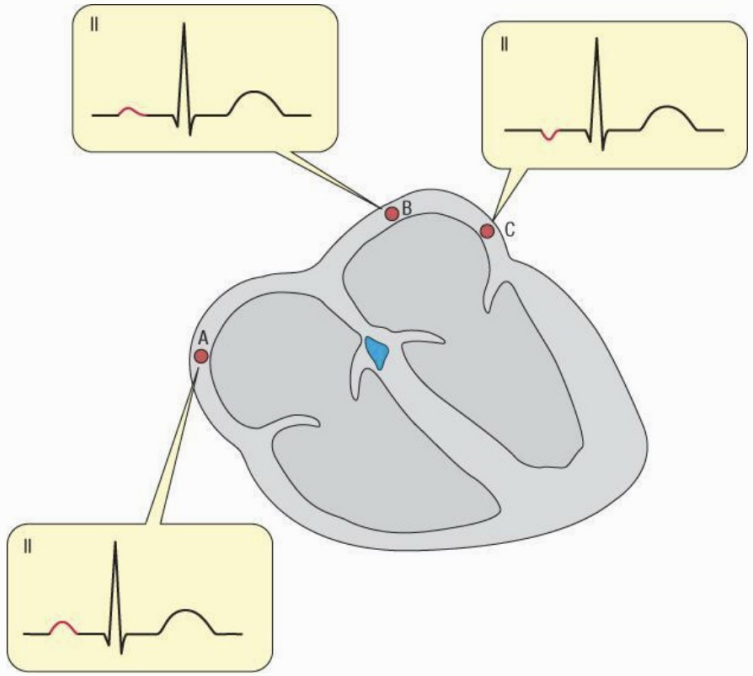


Figura 9-3 Tre diverse morfologie per l'onda P in base alla localizzazione del pacemaker.

Figura 9-7 Un'onda P appuntita e più alta di 2,5 mm nelle derivazioni periferiche indica un'onda P-polmonare.

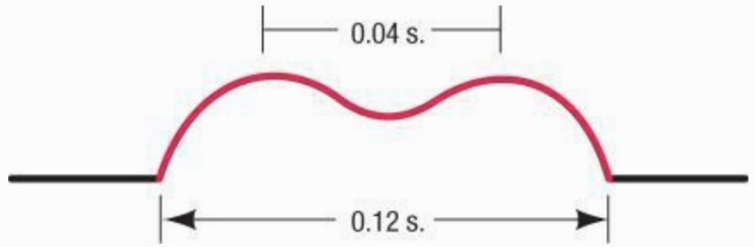
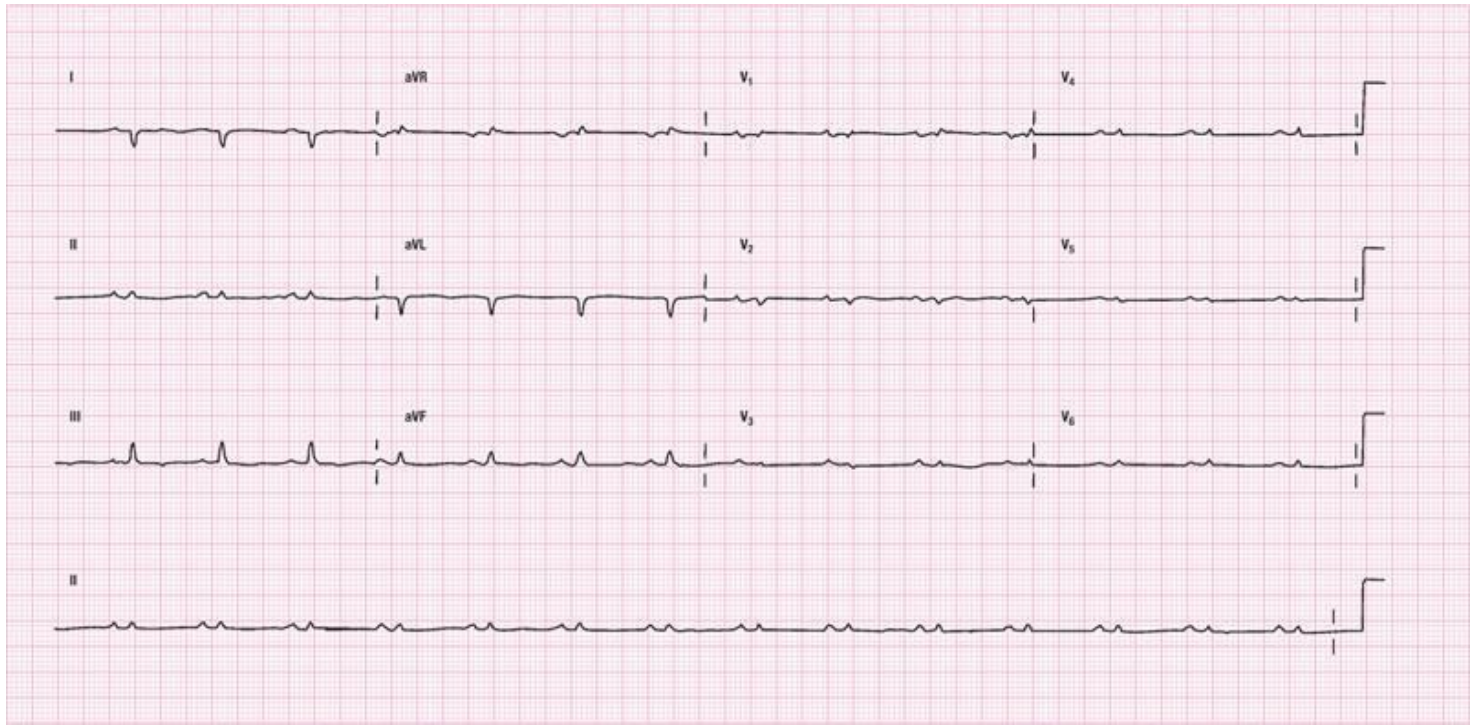
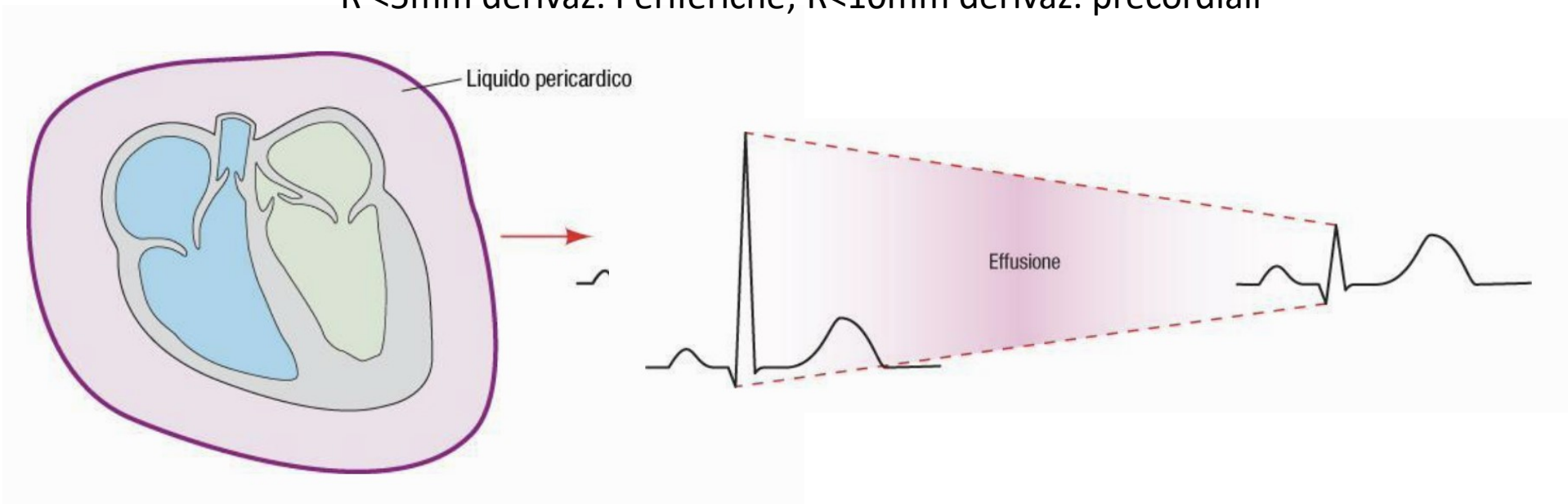
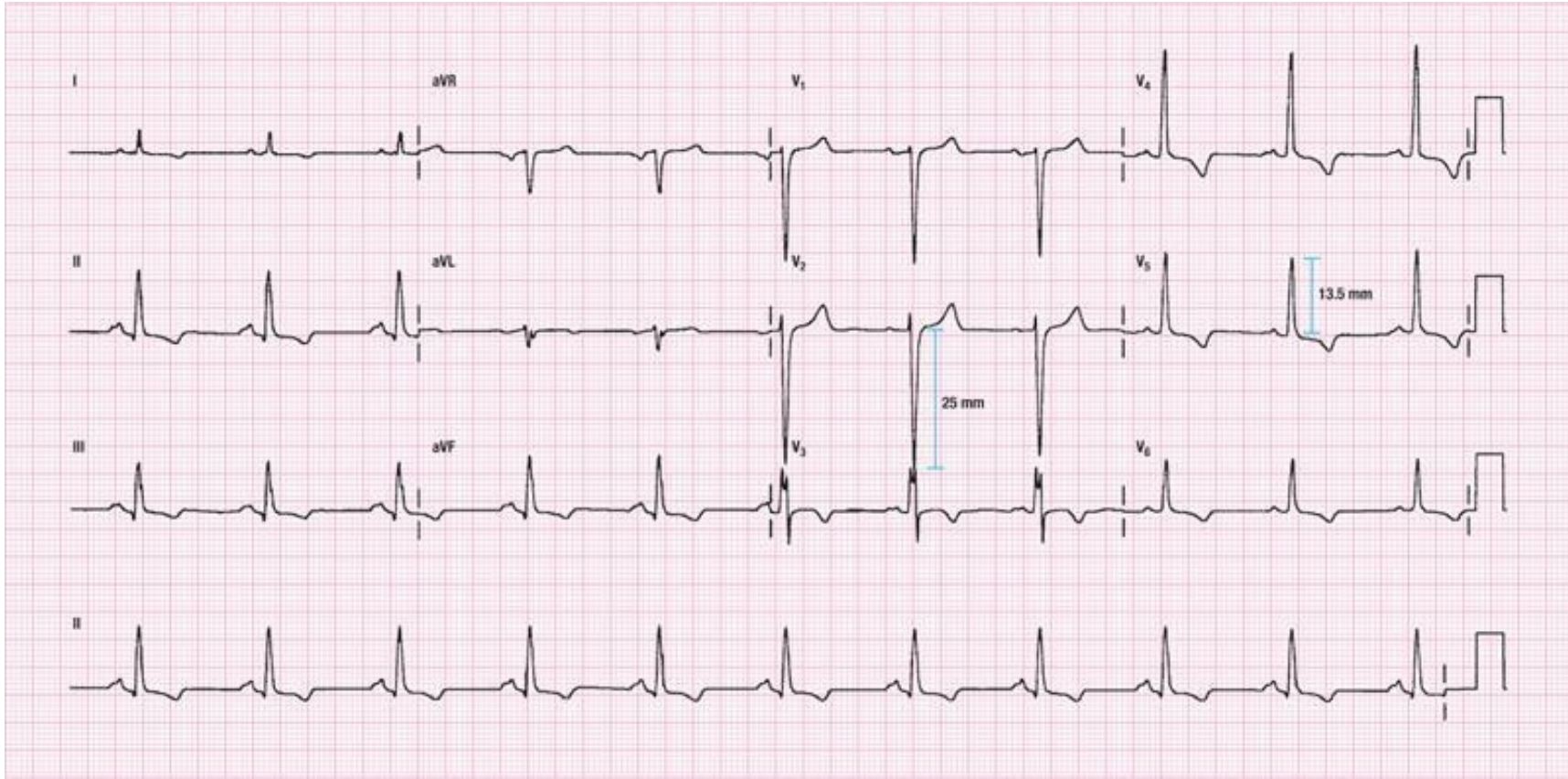


Figura 9-4 Un'onda P con un notch e una durata maggiore di 0,12 secondi nelle derivazioni periferiche, è indicativa di onda P-mitralica.

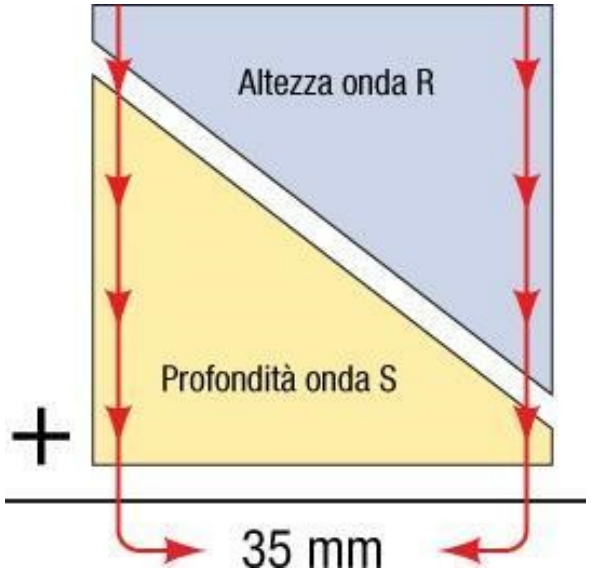


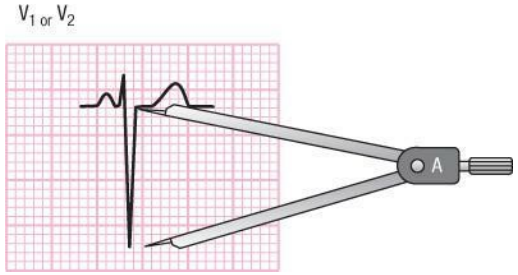
R <5mm derivaz. Periferiche; R<10mm derivaz. precordiali

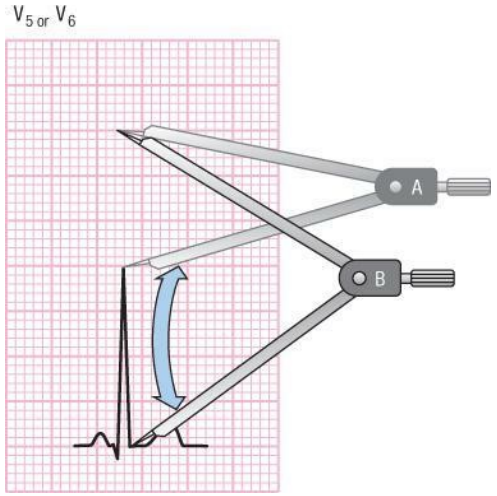


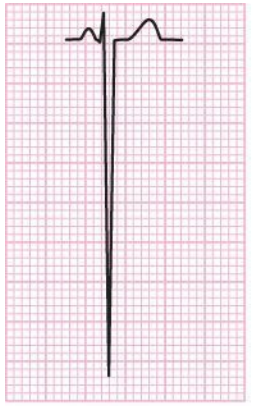

I
aVR
V1
V4
II
aVL
V2
V5
13.5 mm
25 mm
III
aVF
V3
V6
II

Criteri per Ipertrofia Vsx



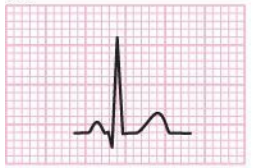






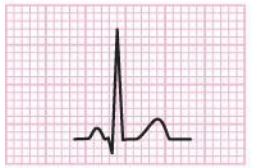
Qualsiasi derivazione precordiale ≥45 mm

aVL



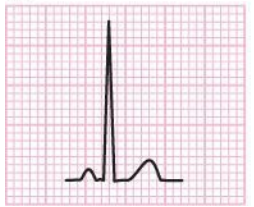
aVL ≥11 mm

I



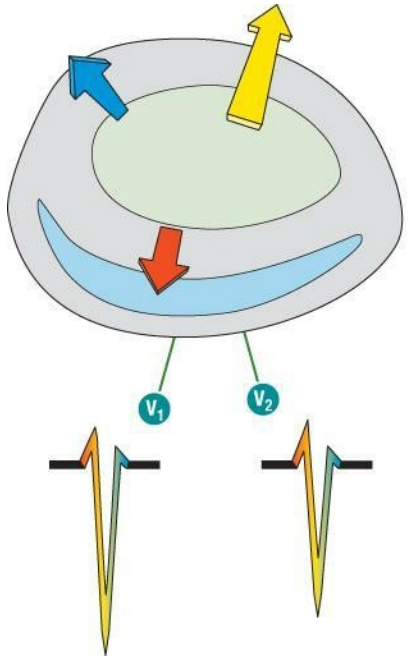
I ≥12 mm

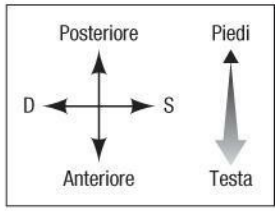
aVF

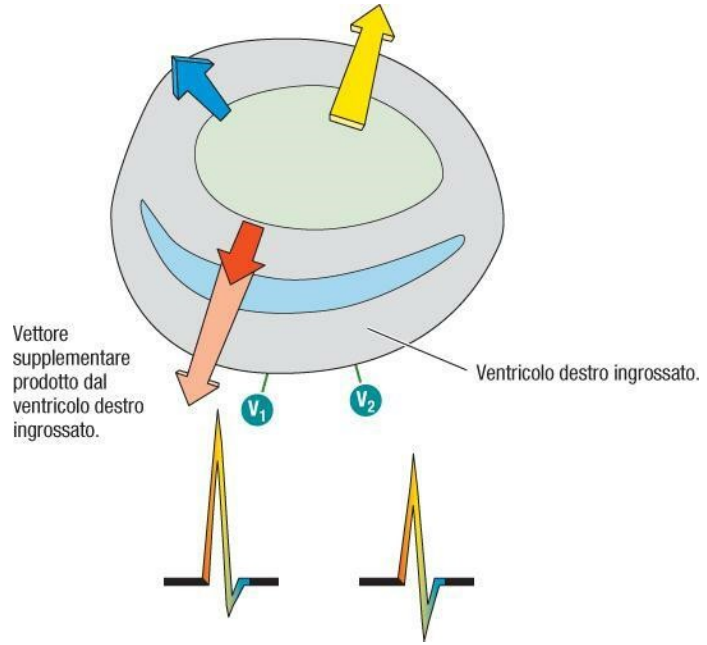


aVF ≥20 mm

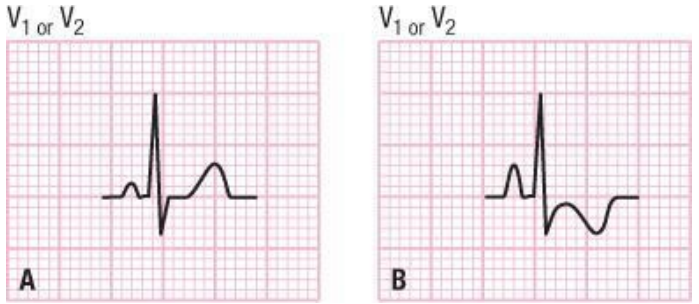
Criterio per Ipertrofia Vdx

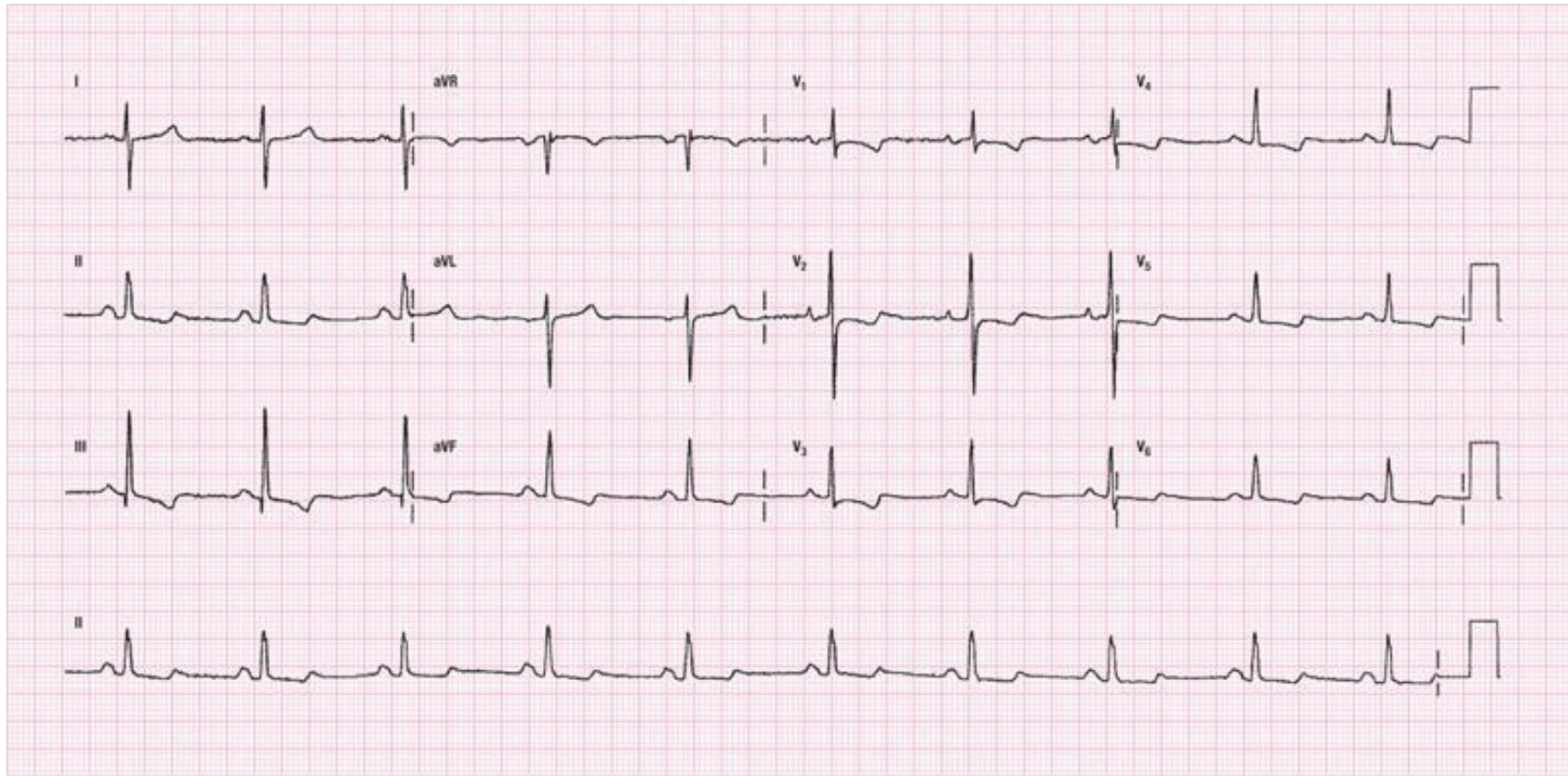




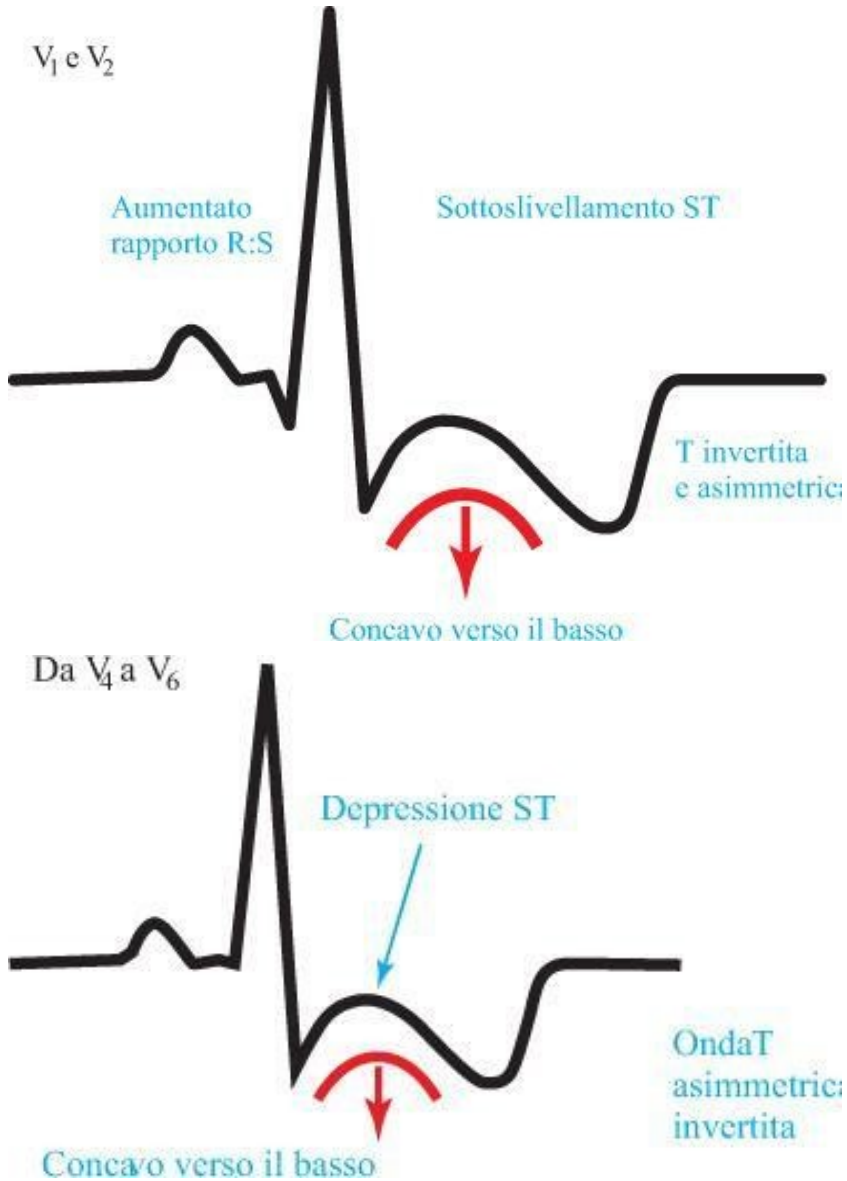


R/S >1 in V1-V2

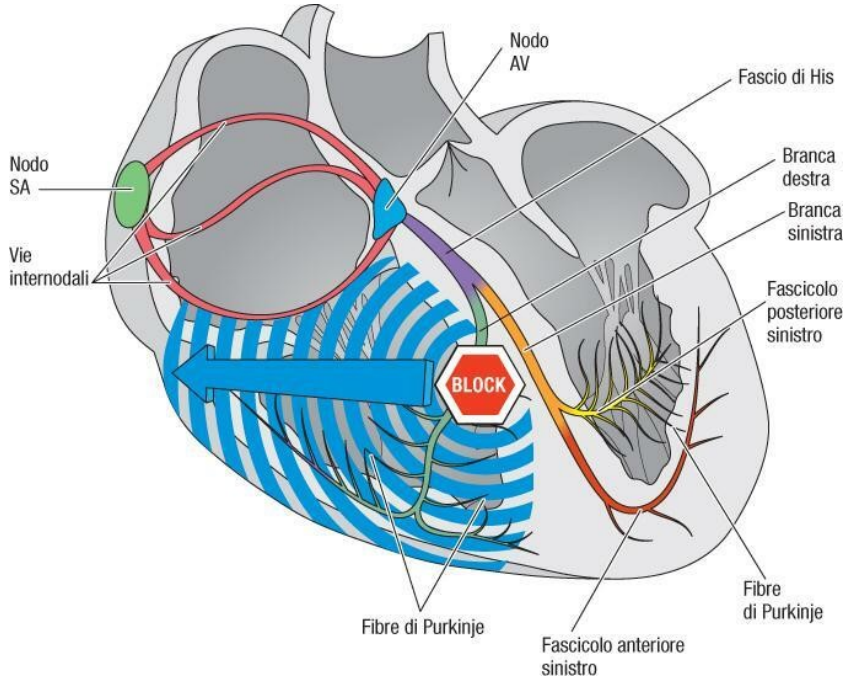


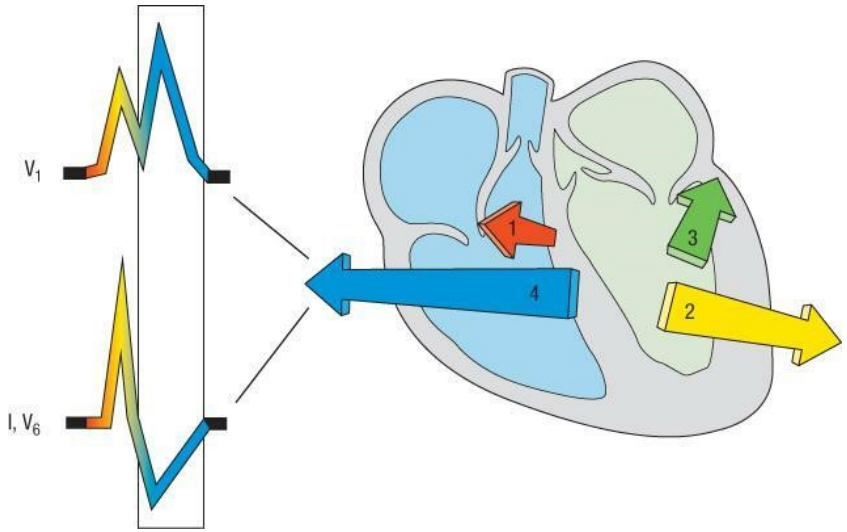

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

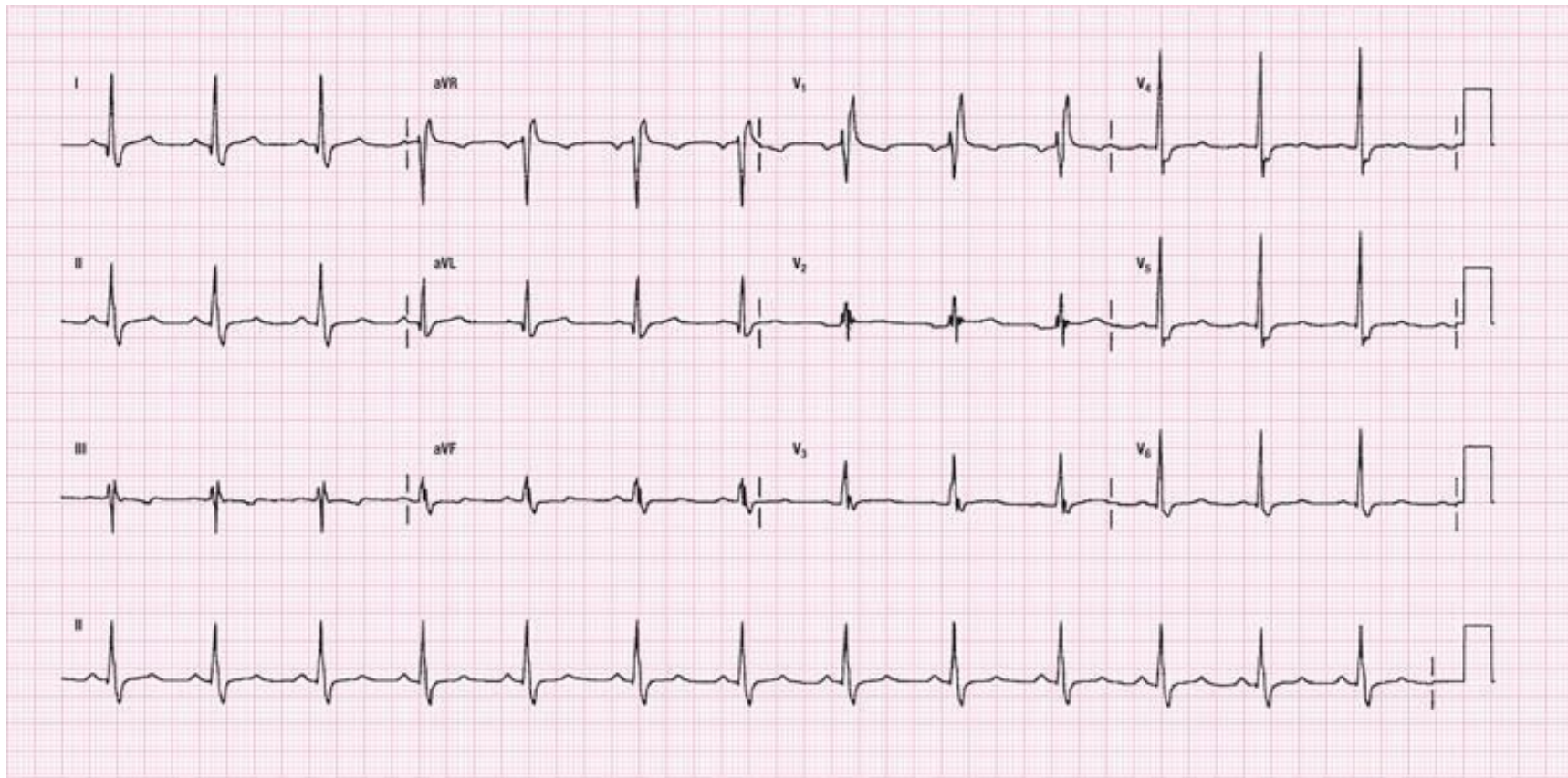
Pattern di strain ventricolare



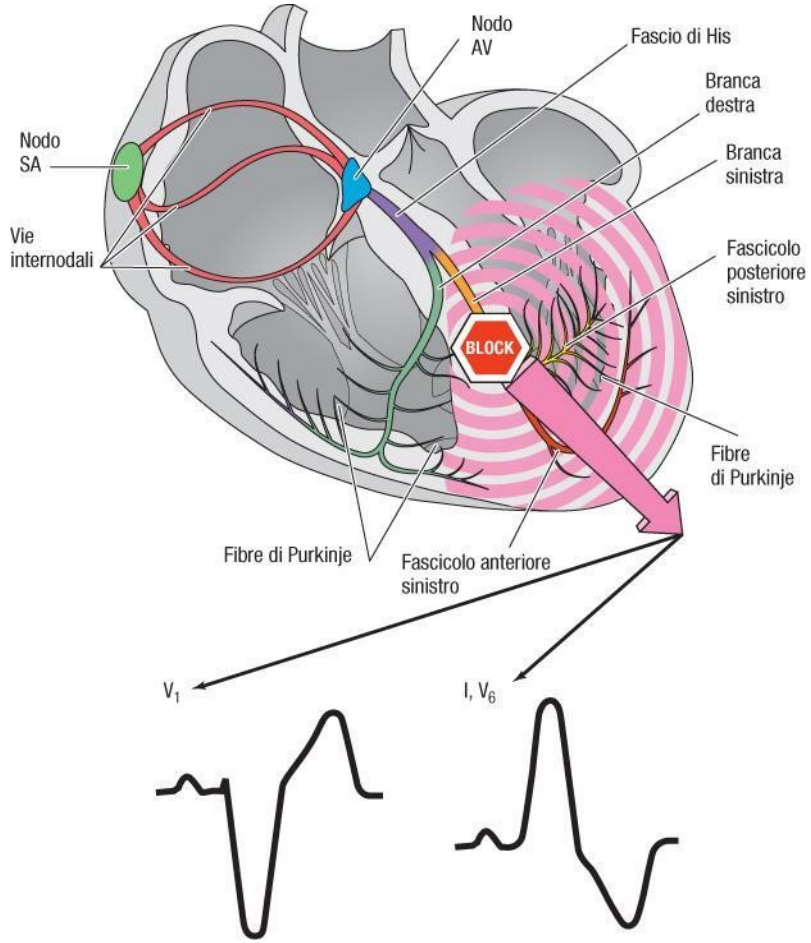
Blocco di Branca Dx

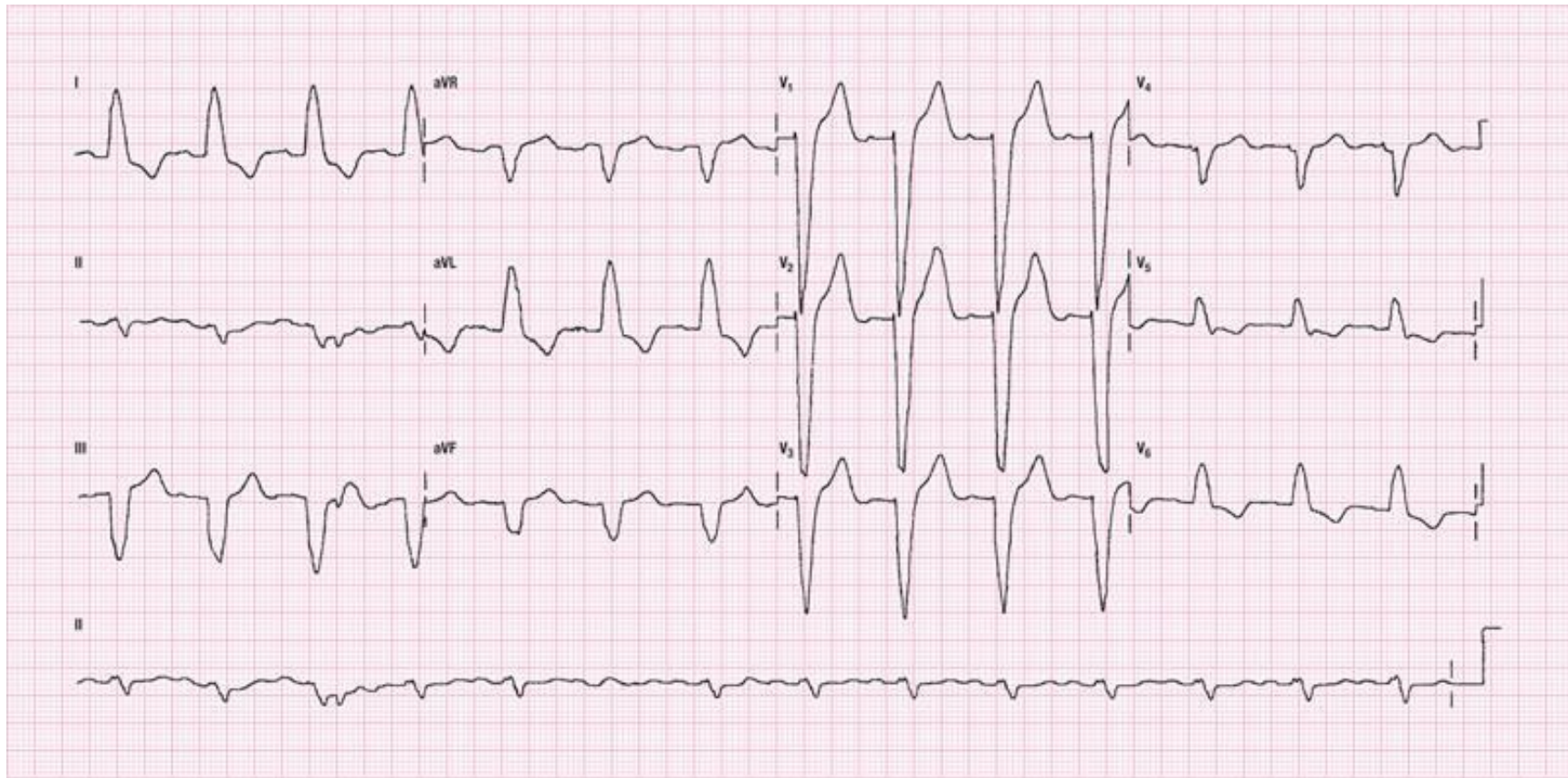




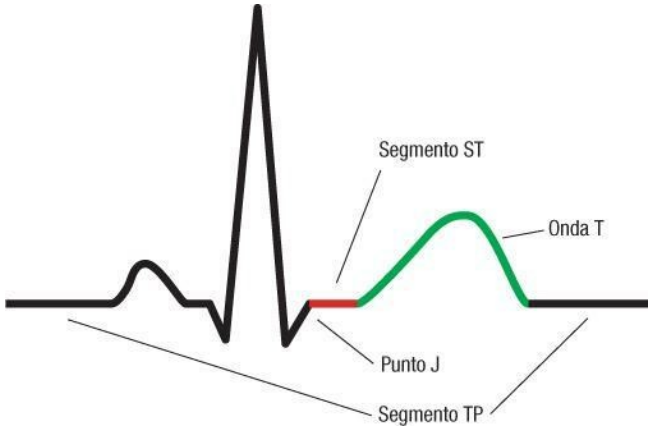

I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

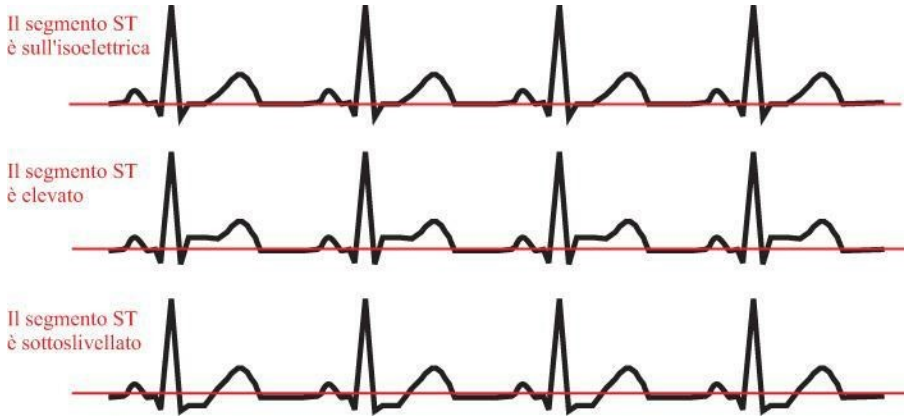
Blocco di Branca Sx




I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
II

Anomalie della Ripolarizzazione (ST-T)





ECG nella Cardiopatia Ischemica

ISCHEMIA

T invertite

ST sopraslivellato

onde Q

NECROSI

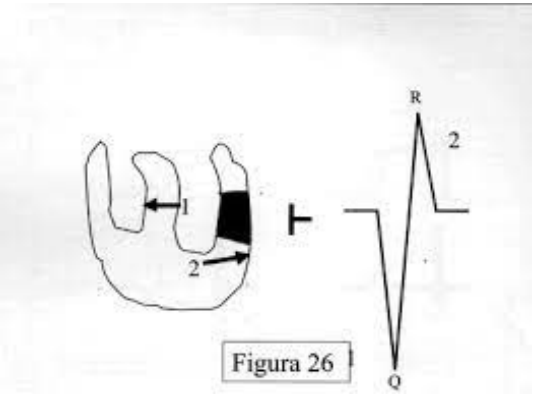
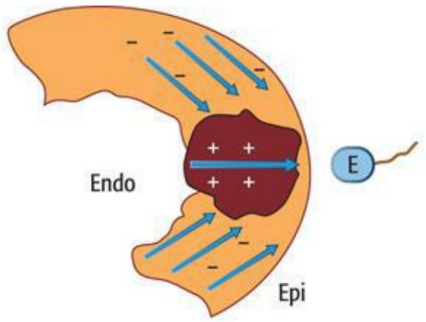
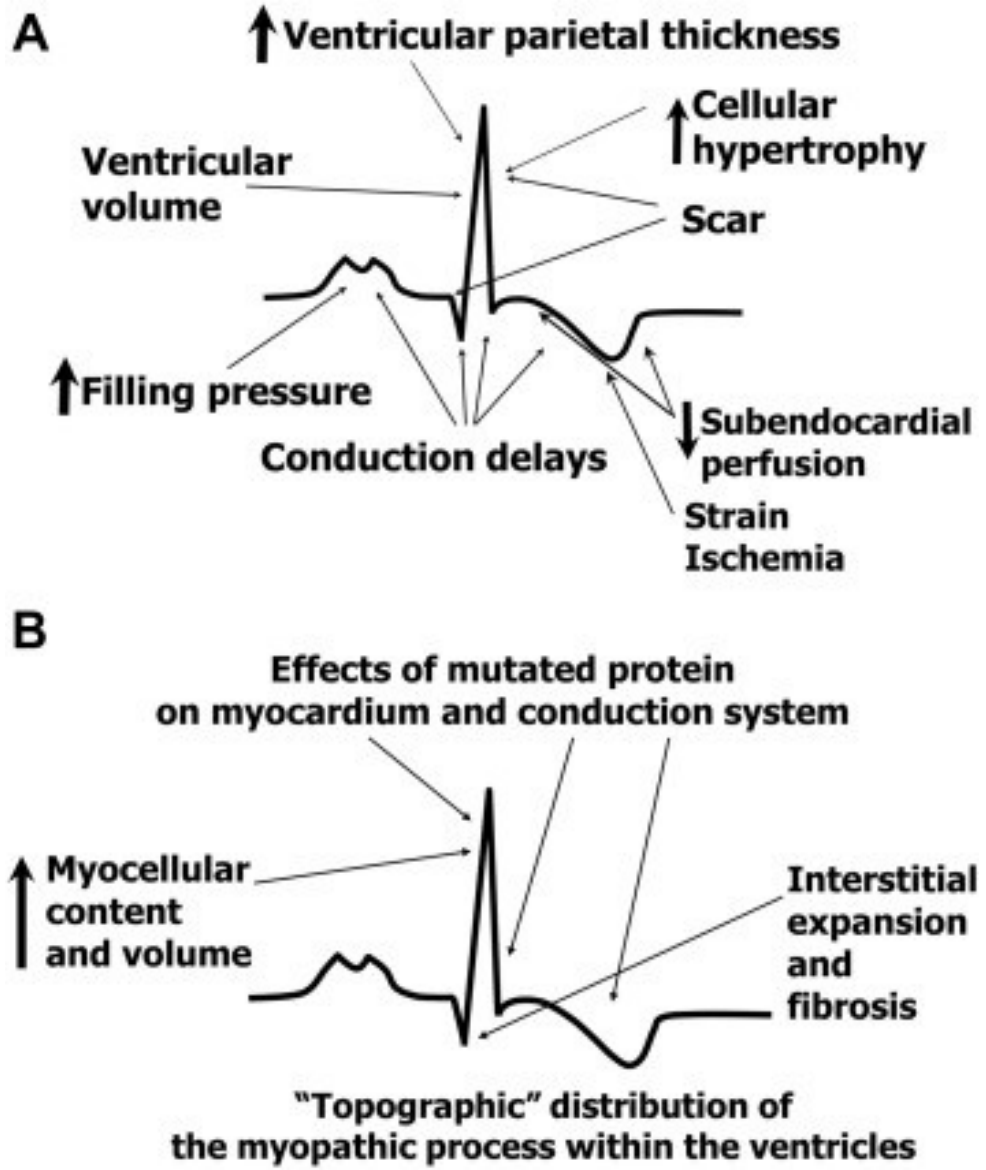


Figura 26

LESIONE

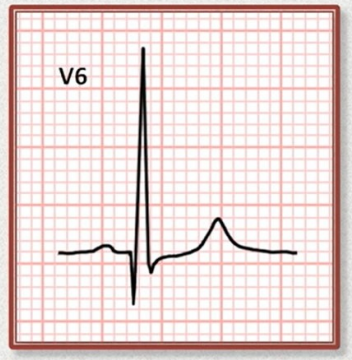


ECG: red flags per il sospetto clinico



Hypertrophic Cardiomyopathy

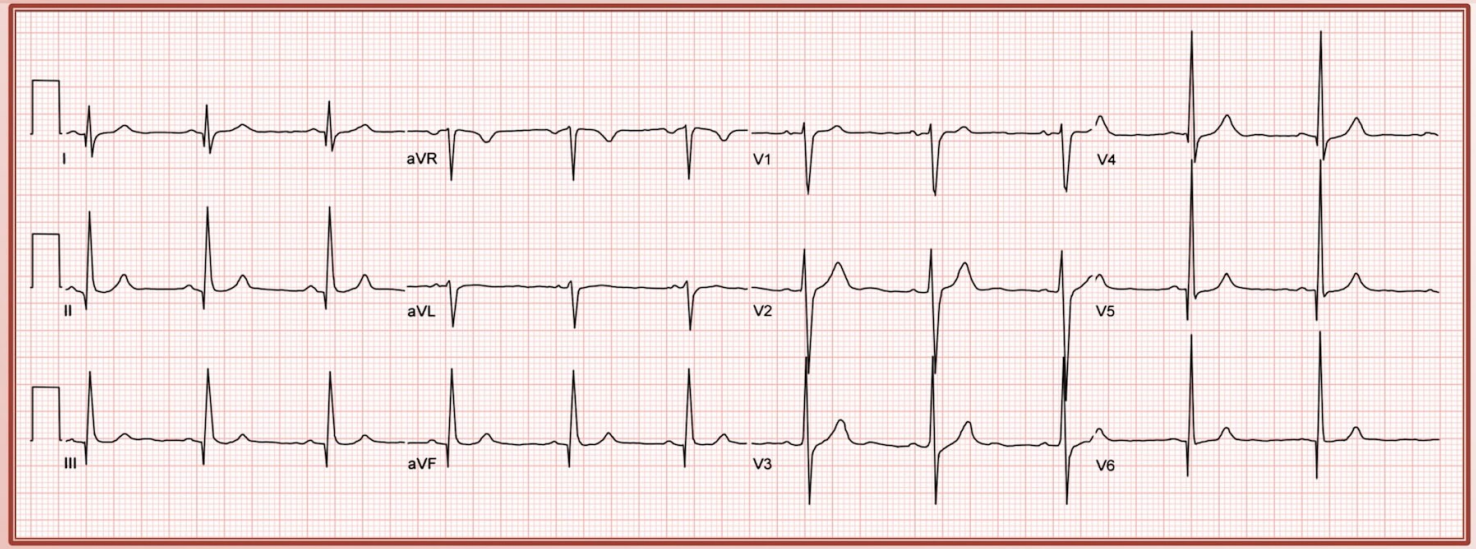
EKG Characteristics

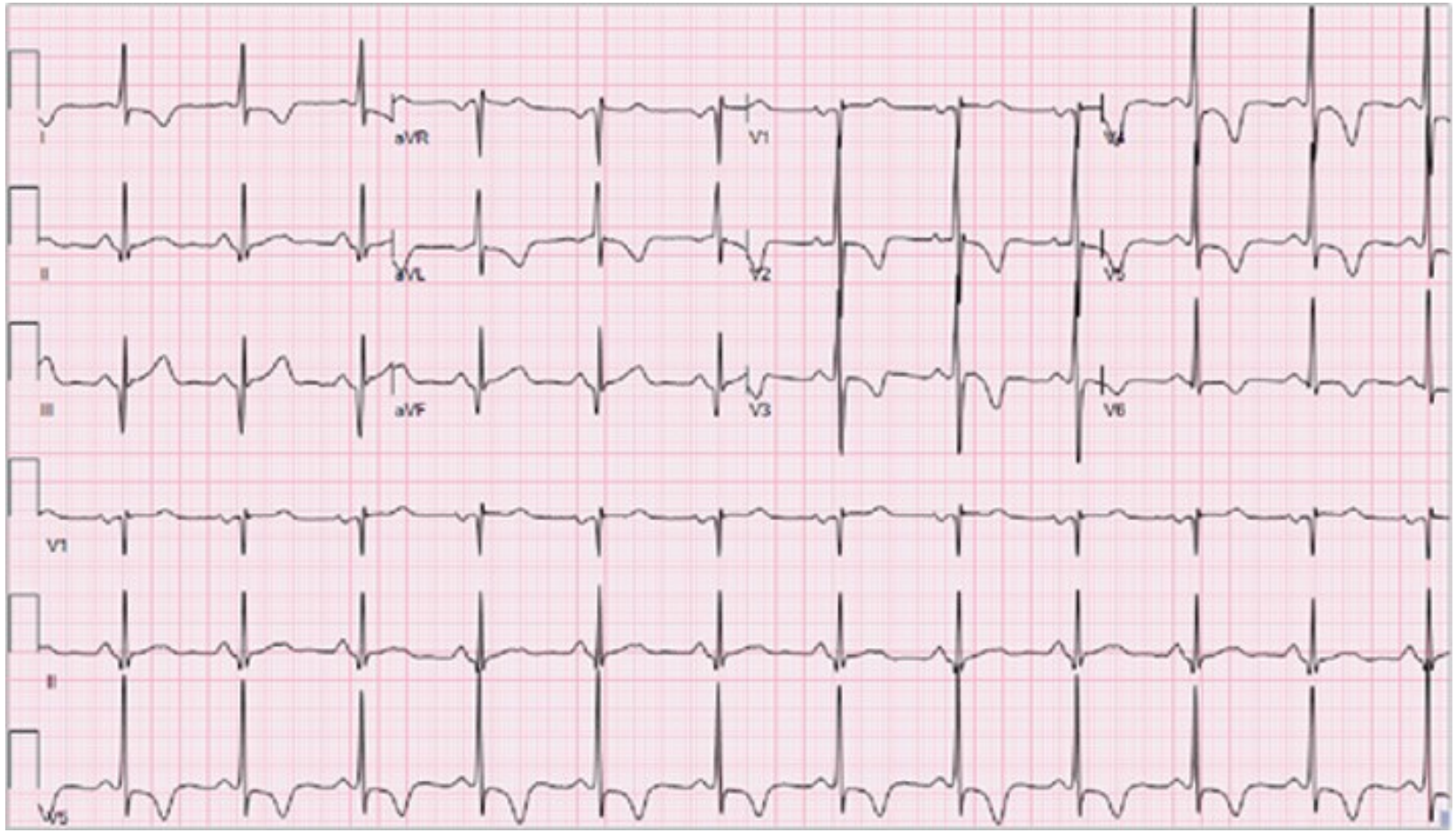


Deep and narrow Q waves secondary to septal hypertrophy typical of HCM

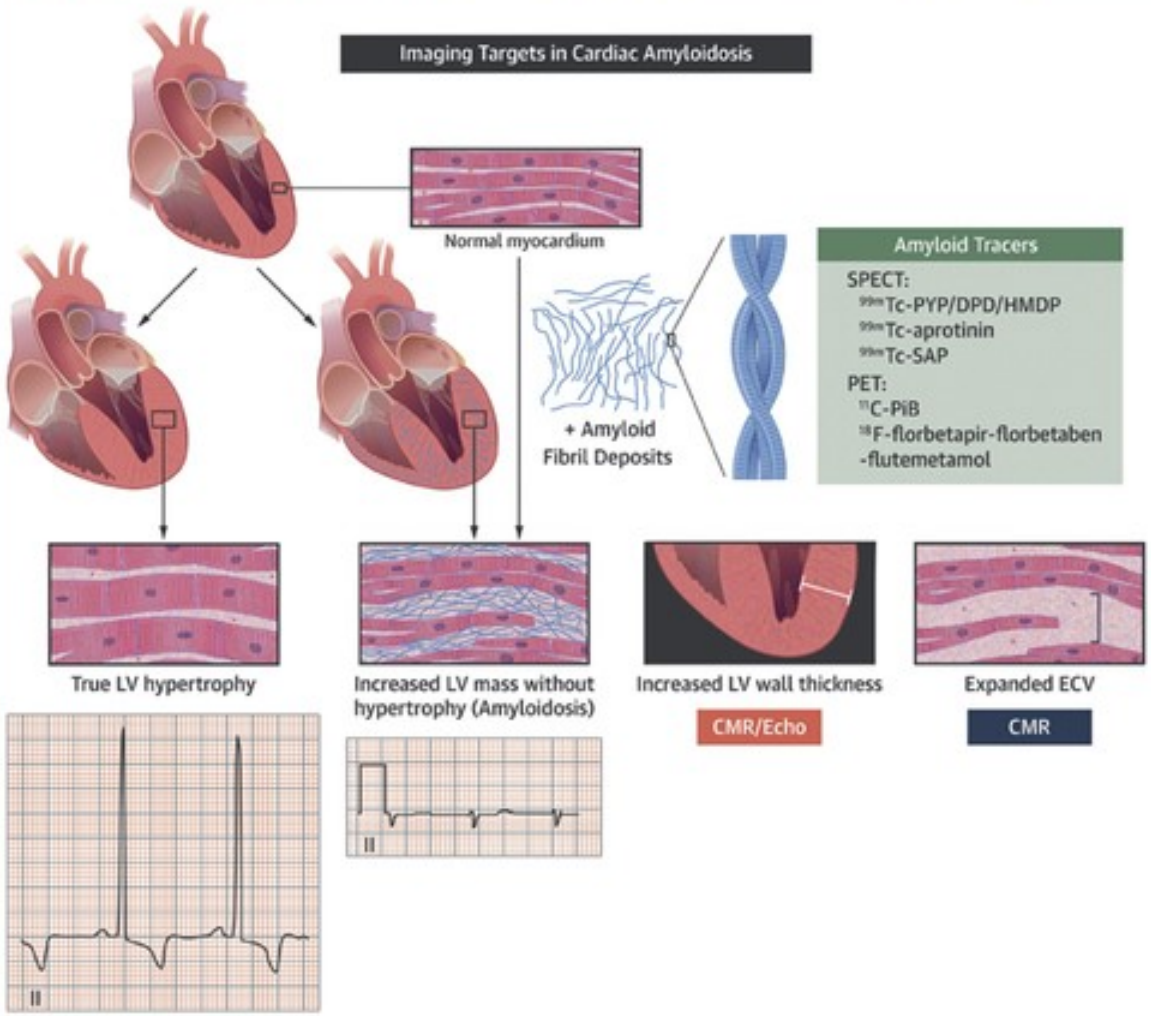
Typical EKG findings may include:

- Deep and narrow Q waves in the lateral and inferior leads
- General signs of LVH (high QRS voltage with widespread repolarization abnormalities)
- Deeply inverted T waves in the precordial leads are seen in the apical variant

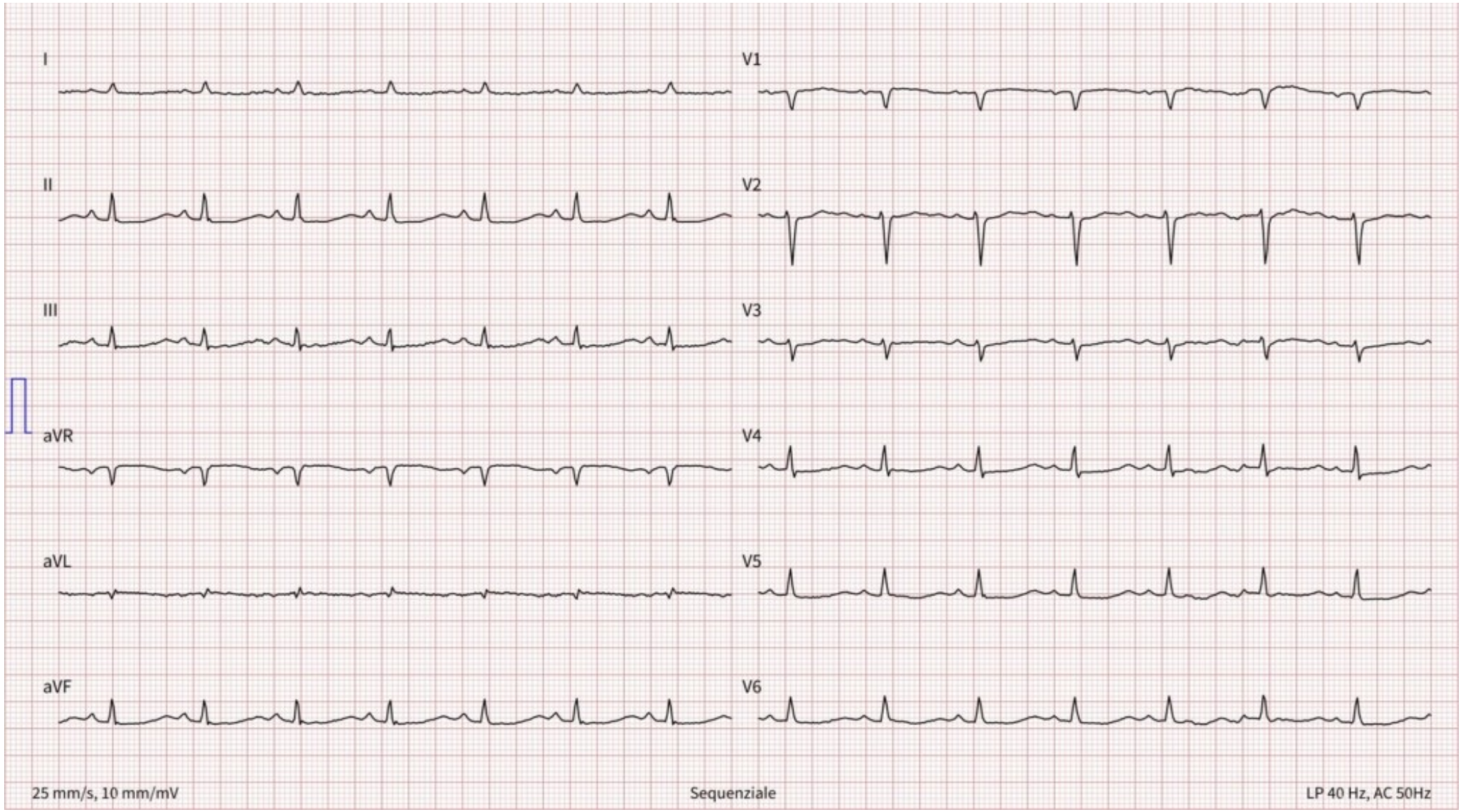



I
aVR
V1
II
aVL
V2
III
aVF
V3
V6
V1
II
V5

CENTRAL ILLUSTRATION: Imaging Targets in Cardiac Amyloidosis



Dorbala, S. et al. J Am Coll Cardiol Img. 2020;13(6):1368-83.


I
II
III
aVR
aVL
aVF
V1
V2
V3
V4
V5
V6
25 mm/s, 10 mm/mV
Sequenziale
LP 40 Hz, AC 50Hz

ECG e Malattia di Anderson-Fabry

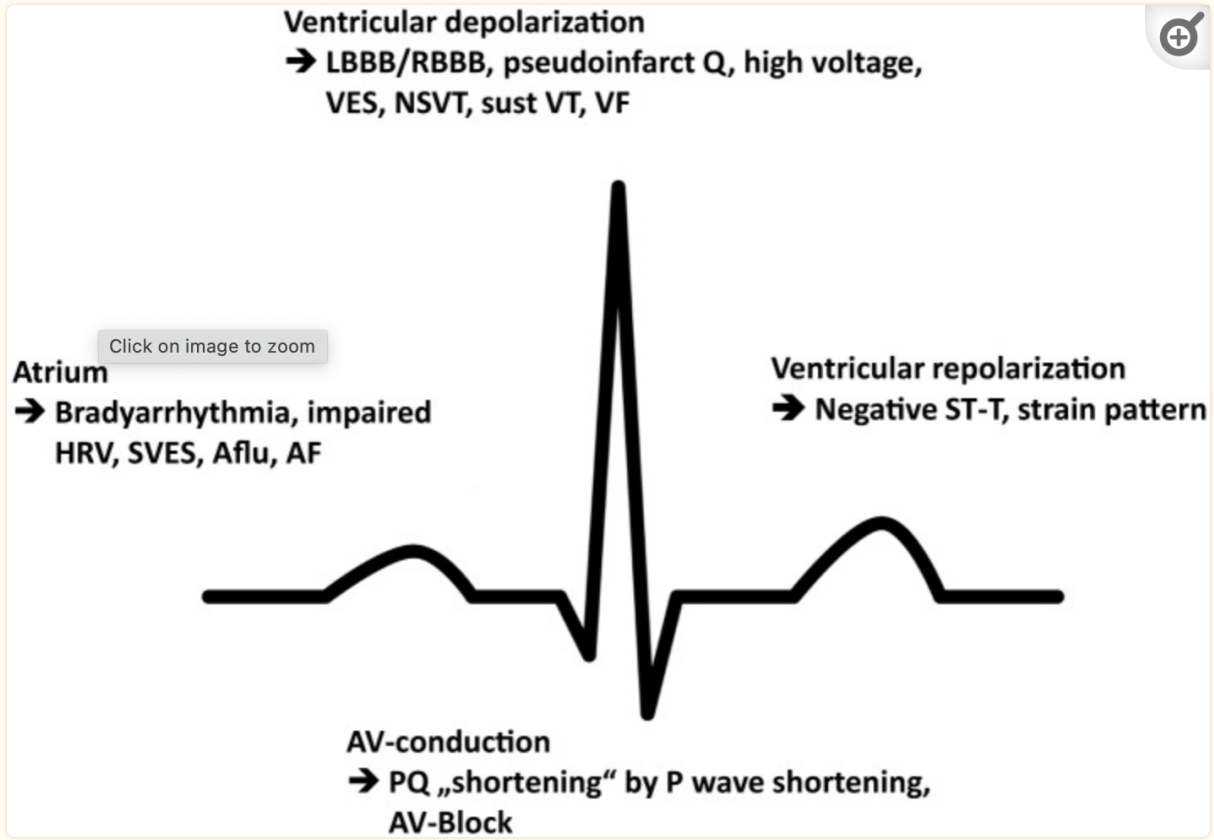


Figure 2

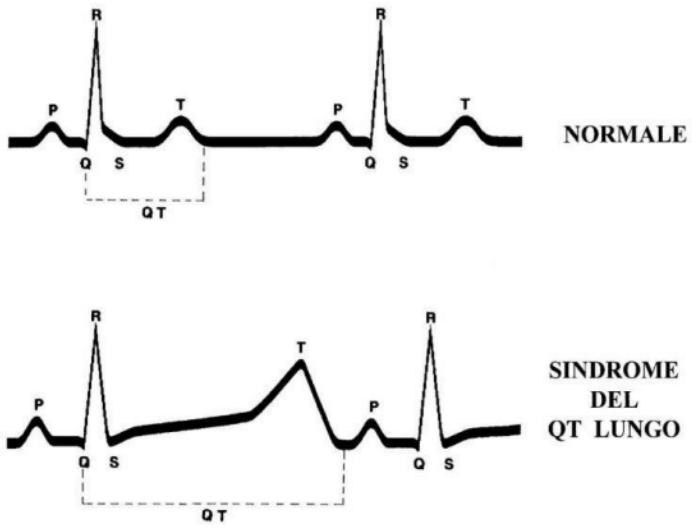
Schematic illustration of the most prevalent conduction abnormalities and arrhythmia. HRV, heart rate variability; SVES, supraventricular extrasystole; Aflu, atrial flutter; AF, atrial fibrillation; LBBB, left bundle branch block; RBBB, right bundle branch block; VES, ventricular extrasystole; NSVT, non-sustained ventricular tachycardia; sust VT, sustained ventricular tachycardia; VF, ventricular fibrillation.

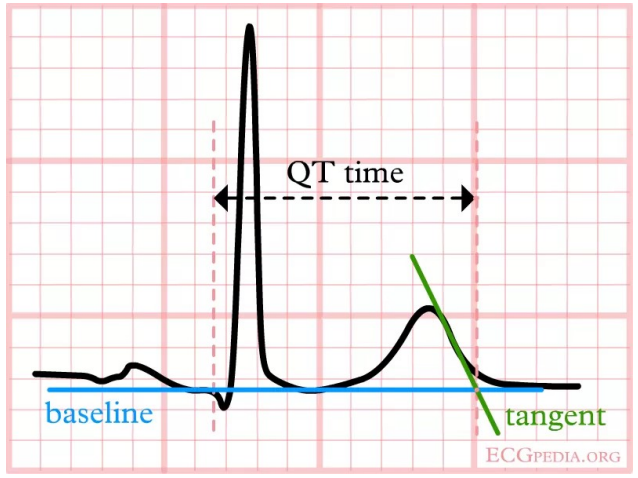
L'INTERVALLO QT

(fase di ripolarizzazione)

Rappresenta la sistole elettrica: tempo necessario perché avvengano la depolarizzazione e la ripolarizzazione ventricolare.

- **Varia al variare della frequenza cardiaca (QT corretto, QTc).**
- **Valori normali di QTc sono compresi tra 350-440 msec.**

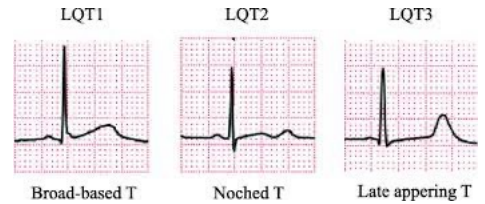




Basi genetiche della sindrome del QT lungo

Basi genetiche: nella maggior parte dei casi, LQTS è trasmessa con modalità autosomica dominante, raramente è ereditata con modalità autosomica recessiva.

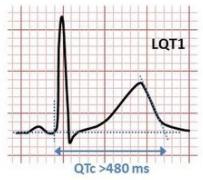
Forme più comuni
(circa 75%)



LQT1
il *gene* mutato è ***KCNQ1*** che codifica per il canale K^+ Kv7.1

onde T con ampia base

provoca aritmia soprattutto durante esercizio (maggiormente nel nuoto)



LQT2
il *gene* mutato è ***KCNH2*** che codifica per il canale K^+ Kv11.1

onde T dentellate di piccola ampiezza o bifasiche

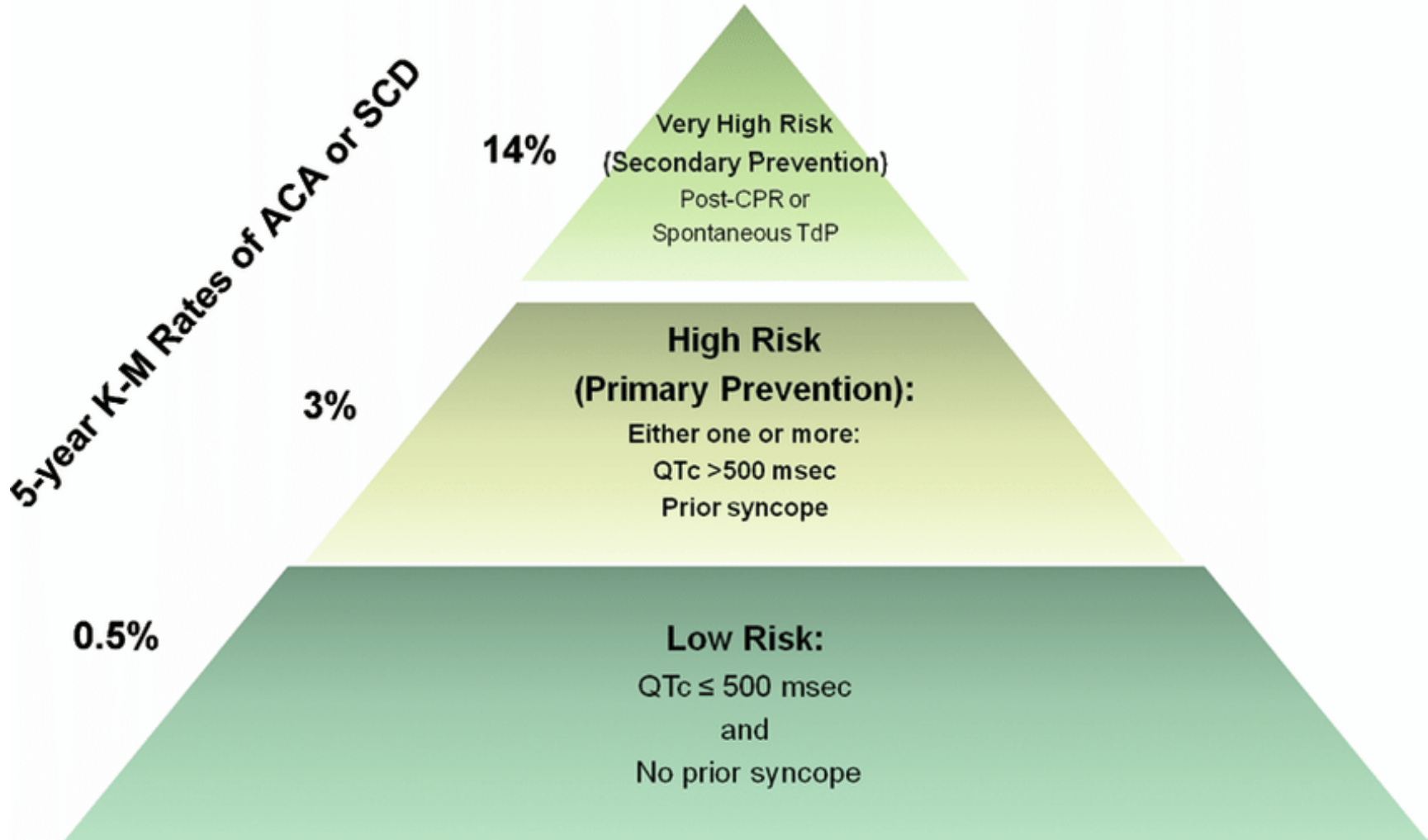
provoca aritmia innescata da stimoli improvvisi o uditivi

LQT3:
il *gene* mutato è ***SCN5A*** che codifica per il canale Na^+ Nav1.5

lungo segmento isoelettrico seguito da onda T a base stretta

provoca aritmia soprattutto durante il sonno

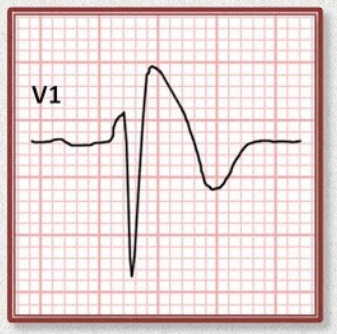
Risk Stratification for ACA or SCD in LQTS Patients



Brugada Syndrome

EKG Characteristics

Patients with Brugada have a pseudo-RBBB and persistent ST elevations in V1-V2.

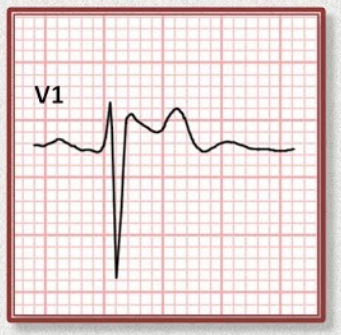


Type 1

ST elevations ≥ 2mm

Downsloping ST segment

Inverted T wave



Type 2

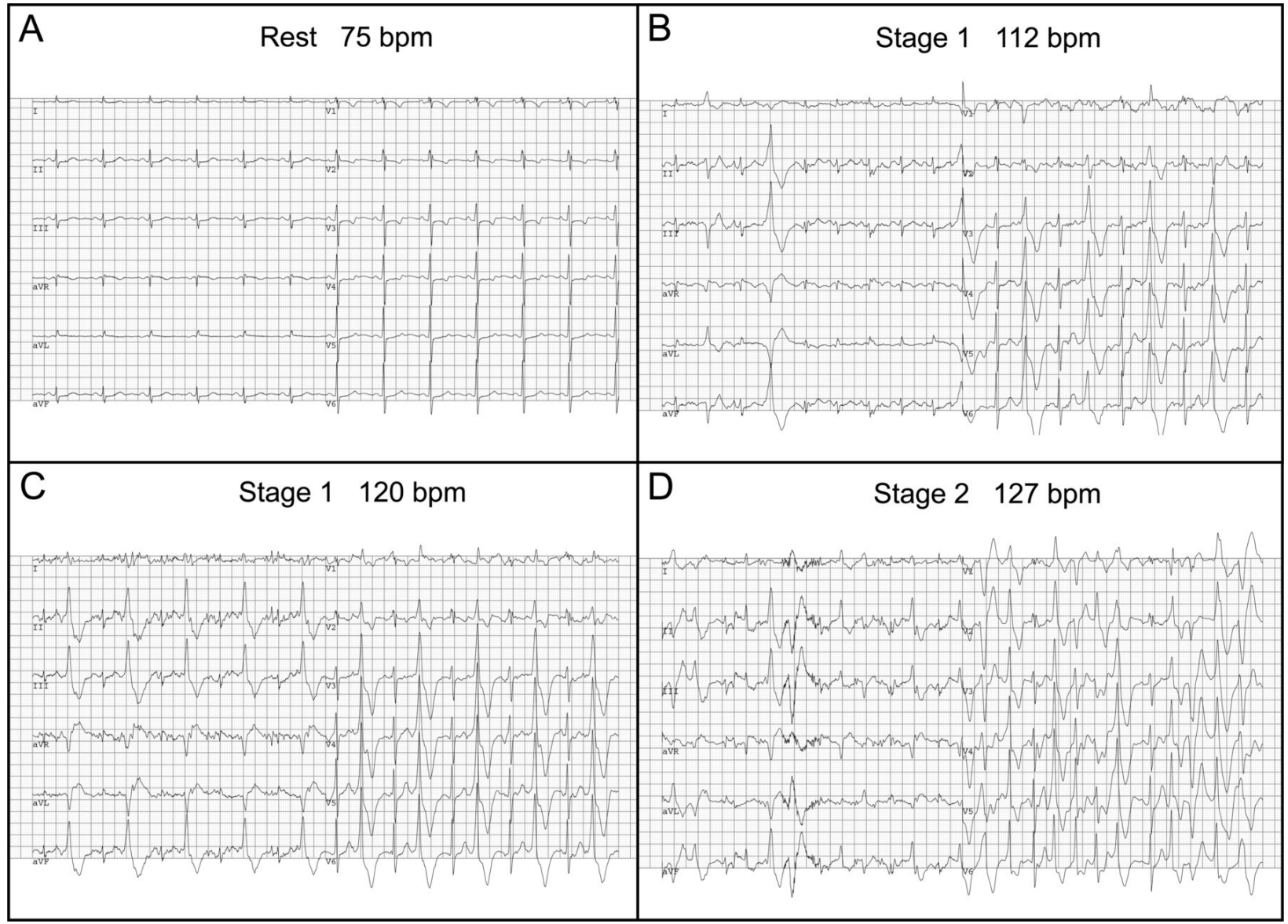
ST elevations ≥ 2mm

"Saddle back" ST-T wave configuration

Upright or biphasic T wave

Tachicardia ventricolare polimorfa catecolaminergica (CPVT)

- La **tachicardia ventricolare polimorfa catecolaminergica** (CPVT) è una malattia su base genetica, caratterizzata dall'insorgenza di aritmie (battito cardiaco irregolare) in occasione di esercizio fisico o emozioni improvvise.


A
Rest 75 bpm
B
Stage 1 112 bpm
C
Stage 1 120 bpm
D
Stage 2 127 bpm

ECG nelle Cardiomiopatie

Table 3 **Electrocardiographic abnormalities that suggest specific diagnoses, grouped according to the main cardiac phenotype**

Main phenotype	Finding	Specific diseases to be considered
HCM	Short P-R /preexcitation	Glycogenosis; Danon disease; PRKAG2; Anderson–Fabry disease
		Mitochondrial disease
	AV block	Amyloidosis
		Late-stage Anderson–Fabry disease
		Danon disease
		Acute myocarditis
	Extreme LVH (Sokolow >100)	Danon disease; Pompe
	Low QRS voltage (or normal voltages despite increased LV wall thickness)	Amyloidosis
	Extreme superior ('North-West') QRS axis deviation	Noonan syndrome
DCM	AV block	Laminopathy
		Emery Dreifuss 1
		Myocarditis, particularly Trypanosoma cruzi, Diphtheria and Lyme disease
		Sarcoidosis
		Desminopathy
		Myotonic dystrophy
	Low P wave amplitude	Emery Dreifuss 1 and 2
	Atrial standstill	Emery Dreifuss 1 and 2
	'Posterolateral infarction'	Dystrophin-related cardiomyopathy
		Limb-girdle muscular dystrophy
		Sarcoidosis
	Low QRS voltage + 'atypical RBBB'	ARVC with biventricular involvement
	Extremely low QRS amplitude	PLN mutation (very rare)
ARVC	Inverted T waves in inferolateral leads	ARVC with biventricular involvement
	Epsilon waves in inferolateral leads	ARVC with biventricular involvement
RCM	AV block	Desmin-related cardiomyopathy
		Amyloidosis

ARVC, arrhythmogenic right ventricular cardiomyopathy; AV, atrioventricular; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; PLN, phospholamban; RBBB, right bundle branch block; RCM, restrictive cardiomyopathy.

Esami di laboratorio nelle Cardiomiopatie

Table 5 **Abnormalities in routine laboratory tests that should raise suspicion of specific cardiomyopathies, grouped according to the main cardiac phenotype**

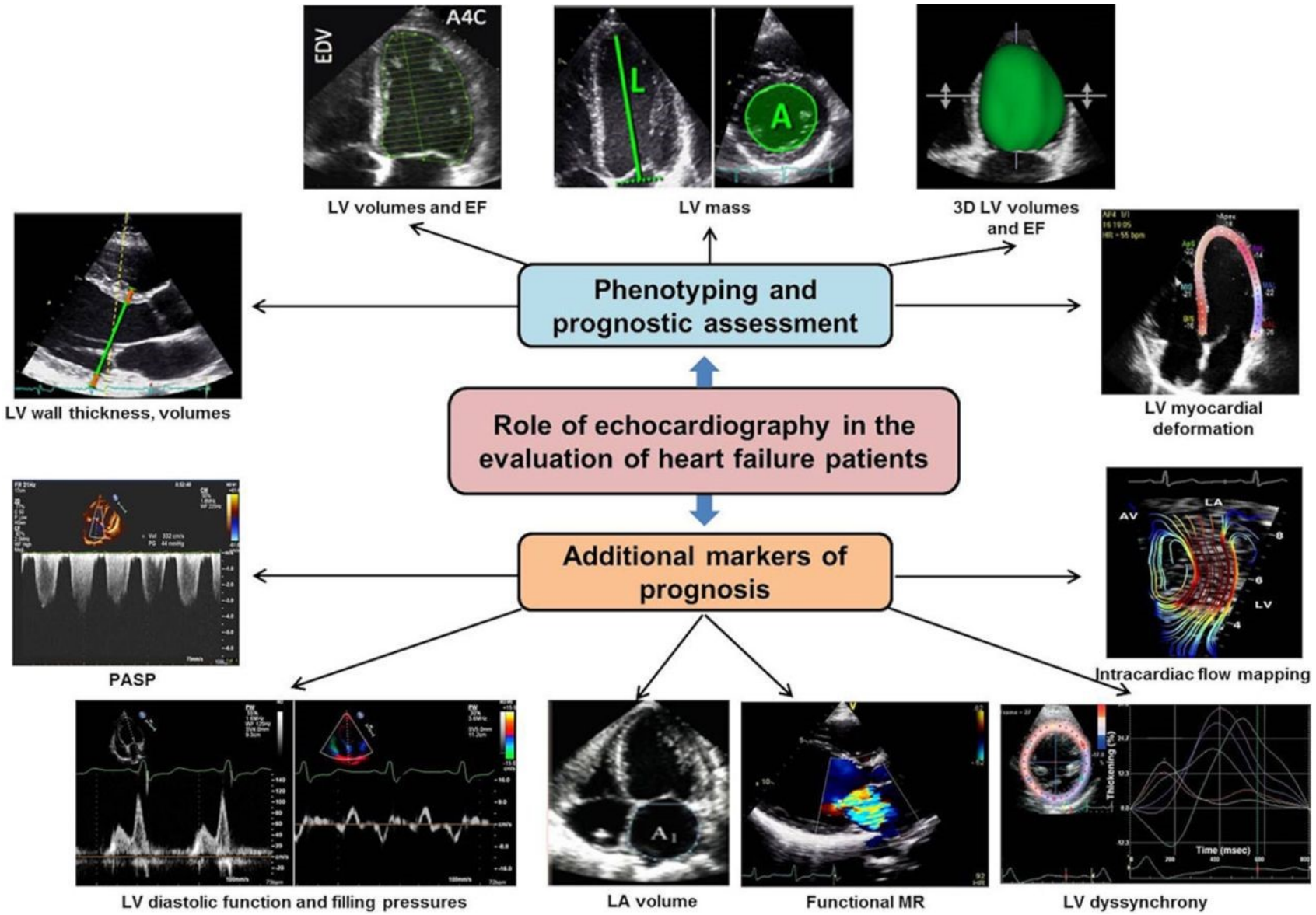
Finding	Main cardiac phenotype		
	HCM	DCM	RCM
↑ Creatine kinase	Mitochondrial diseases Glycogenosis Danon disease	Dystrophinopathies Sarcoglycanopathies Zaspopathies (*LDB3* gene) Laminopathies Myotonic dystrophy *FKTN* mutations Desminopathies Myofibrillar myopathies	Desminopathies
Proteinuria with/without ↓ glomerular filtration rate	Anderson–Fabry disease Amyloidosis		Amyloidosis
↑ Transaminase	Mitochondrial diseases Glycogenosis Danon disease		
High transferrin saturation/ hyperferritinaemia		Haemochromatosis	Haemochromatosis
Lactic acidosis	Mitochondrial diseases	Mitochondrial diseases	
Myoglobinuria	Mitochondrial diseases	Mitochondrial diseases	
Leucocytopenia	Mitochondrial diseases (*TAZ* gene/Barth Syndrome)	Mitochondrial diseases (*TAZ* gene/ Barth Syndrome)	

DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

Agenda

1. Malattia rara: Definizione
2. Malattie rare con manifestazioni cardiovascolari
3. Red flags clinici
4. Red flags all'ECG
5. Red flags all'imaging

Potenzialità informative dell'ecocardiografia



Ecocardiografia nelle Cardiomiopatie

Table 6 **Echocardiographic clues to diagnosis grouped according to main morphological phenotype**

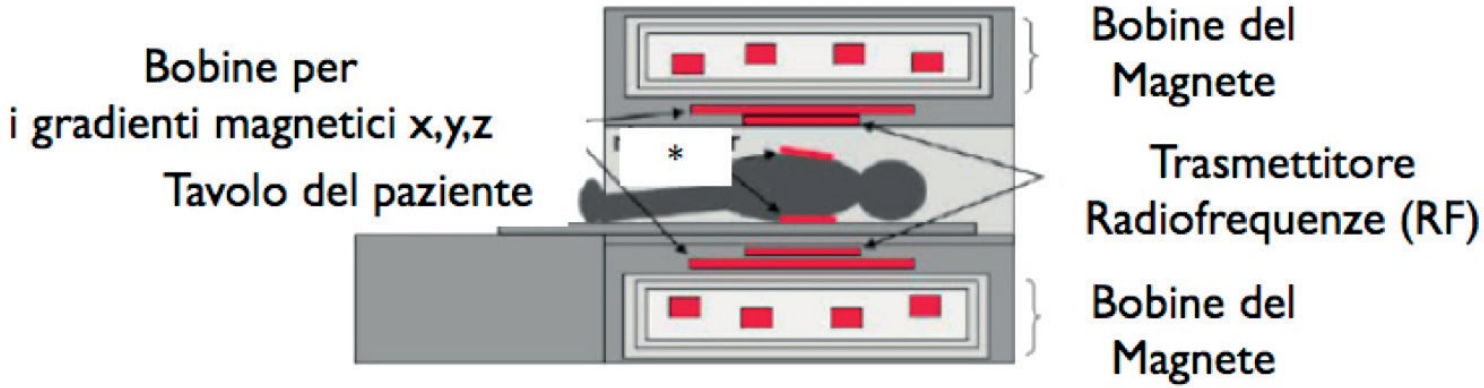
Main cardiac phenotype	Finding	Specific diseases to be considered
HCM	Increased interatrial septum thickness	Amyloidosis
	Increased atrioventricular valve thickness	Amyloidosis; Anderson–Fabry disease
	Increased RV free wall thickness	Amyloidosis, myocarditis, Anderson–Fabry disease
	Mild–moderate pericardial effusion	Amyloidosis, myocarditis
	Ground-glass appearance of ventricular myocardium	Amyloidosis
	Concentric LVH	Glycogenosis, Anderson–Fabry disease
	Extreme concentric LVH	Danon disease, Pompe disease
	Global hypokinesia (with/without LV dilatation)	Anderson– Fabry; mitochondrial disease; TTR-related amyloidosis; PRKAG2 mutations; Danon disease; myocarditis; end-stage sarcomeric HCM
DCM	LV non-compaction	Genetic DCM (more frequently sarcomeric mutations)
	Postero-lateral akinesia/dyskinesia	Dystrophin-related cardiomyopathy
	Mild (absent) dilatation + akinetic/dyskinetic segments with non-coronary distribution	Myocarditis Sarcoidosis
ARVC	Coexistent LV segmental dysfunction	Biventricular ARVC
RCM	Partial LV or RV apical obliteration	Endomyocardial fibrosis/hypereosinophilia

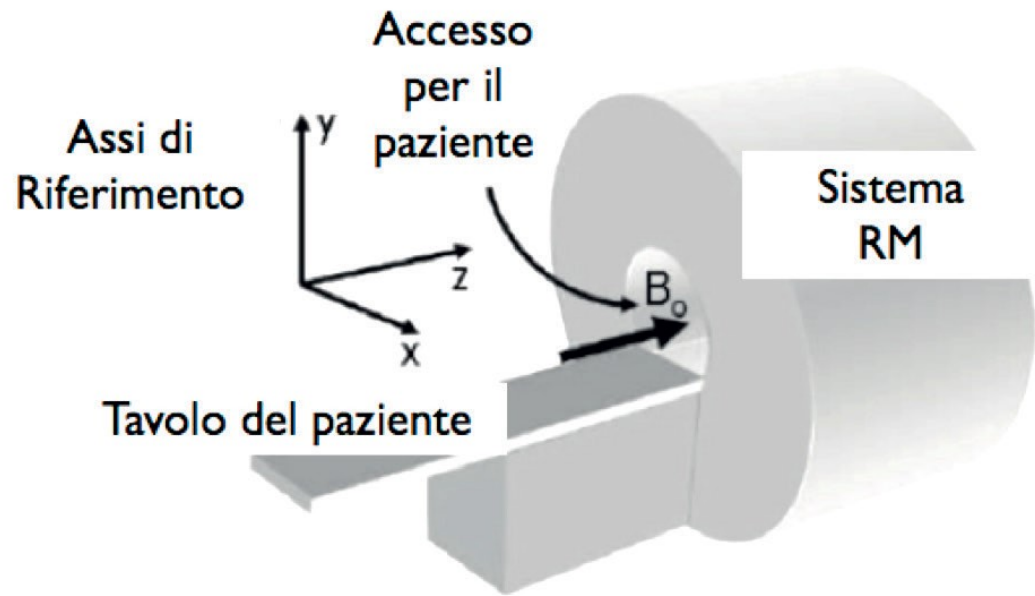
ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LV, left ventricular; LVH, left ventricular hypertrophy; RCM, restrictive cardiomyopathy; RV, right ventricular; TTR, transthyretin.

Principio della RM magnetica

- La RM cardiaca sfrutta le proprietà elettromagnetiche del nucleo dell'idrogeno, un elemento ampiamente rappresentato nel corpo umano in quanto contenuto nell'acqua.
- Il nucleo di idrogeno è costituito da un protone che agisce come un piccolo magnete e che ruota intorno al proprio asse (si dice che ha uno spin).
- Normalmente i protoni sono orientati in modo casuale in tutte le direzioni e pertanto danno origine ad un vettore magnetico nullo.
- Se sottoposti ad un campo magnetico esterno si orientano lungo la direzione del campo magnetico esterno.

*Antenna ricevente per RF





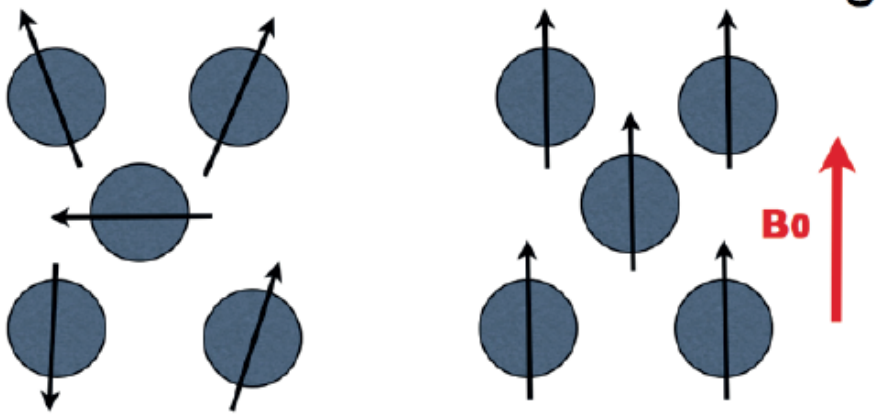
Campo magnetico terrestre, campo magnetico statico in RM a 1,5 Tesla ed atomi di idrogeno

Campo Magnetico Terrestre= 0.2-0.7 Gauss

1 Tesla= 10000 Gauss

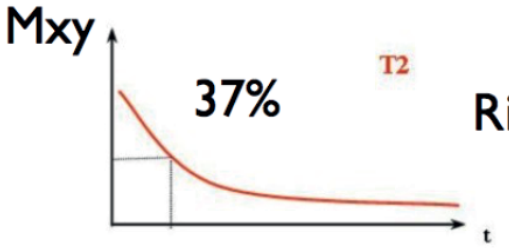
Campo Magnetico in RMC
usualmente 1.5 T
(circa 30000 il campo
magnetico terrestre)

Atomi di idrogeno



Rilassamento

Rilassamento longitudinale o T1



Rilassamento trasversale o T2

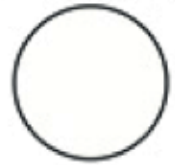
- Alla scomparsa della radiofrequenza i protoni tendono a ritornare nella posizione di equilibrio allineata al campo magnetico principale (rilassamento) secondo tempi caratteristici per ciascun tessuto.
- Tali tempi seguono un andamento esponenziale e sono definiti:

1. ***rilassamento longitudinale o T1*** (spin-reticolo) che definisce la rapidità con cui viene recuperata la magnetizzazione longitudinale. Il tempo T1 è il tempo richiesto per il recupero del 63% della massima magnetizzazione longitudinale;
2. ***rilassamento trasversale o T2*** (spin-spin) che definisce la rapidità con cui decade la magnetizzazione trasversale per la desincronizzazione dei movimenti di precessione. Il tempo T2 è il tempo richiesto per la riduzione al 37% della massima

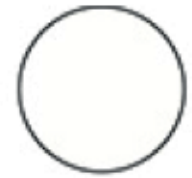
Tissue	T1 (msec)	T2 (msec)
Water/CSF	4000	2000
Gray matter	900	90
Muscle	900	50
Liver	500	40
Fat	250	70
Tendon	400	5
Proteins	250	0.1- 1.0
Ice	5000	0.001

- In base alla loro composizione chimica i tessuti hanno diversi tempi T1 e T2 che possono essere utilizzati per consentire la caratterizzazione tessutale.
- Ad es. i tessuti ricchi di lipidi hanno un tempo T1 breve dovuto alla possibilità di cedere energia rapidamente e ritornare allo stato di base.
- I tessuti a ricco contenuto d'acqua hanno invece tempi T1 e T2 più lunghi.

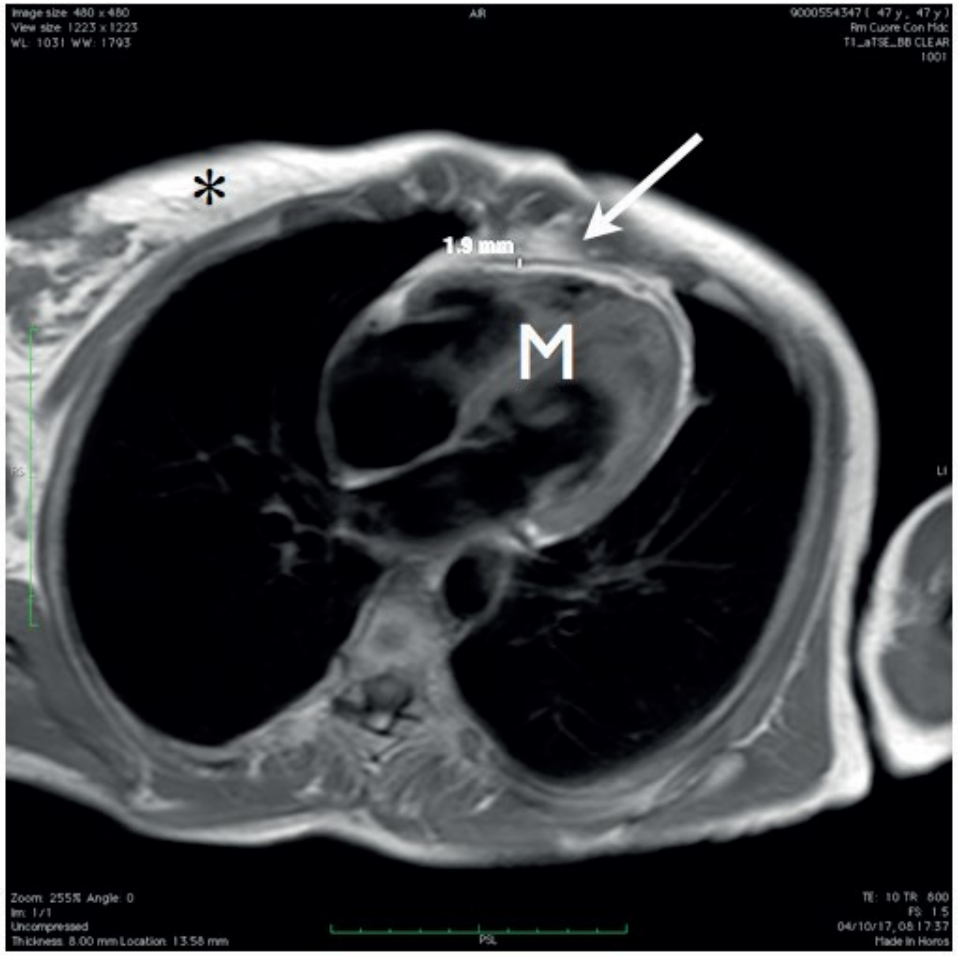
Sequenze T1 pesate

Segnale Assente (Nero)	Basso	Intermedio	Alto (Bianco)
			
Aria, Calcio, Flusso turbolento	Liquidi, Legamenti, Muscoli, Tendini, Organi addominali, Cartilagine	Tessuto ad alto contenuto proteico (ascesso, cisti complessa, fluido sinoviale)	Grasso, Sangue, Gadolinio, Proteine

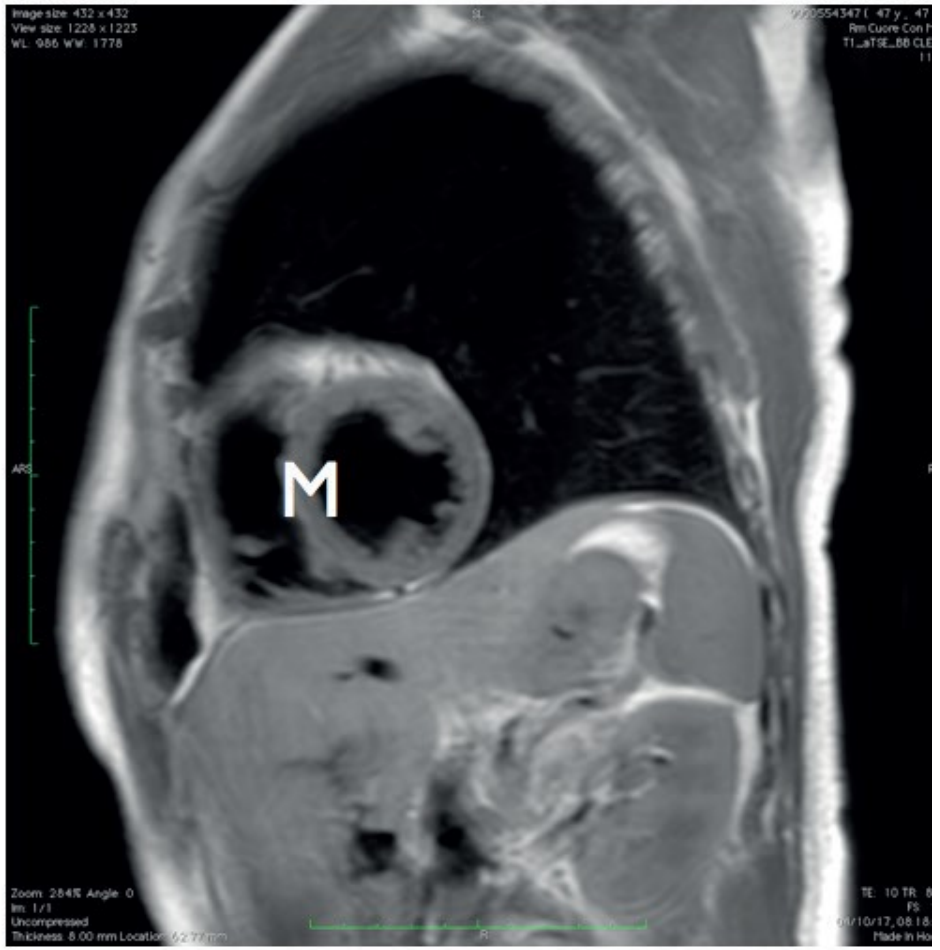
Sequenze T2 pesate

Segnale Assente (Nero)	Basso	Intermedio	Alto (Bianco)
			
Aria, Calcio, Flusso turbolento	Legamenti, Tendini, Fegato, Pancreas, Surreni, Cartilagine	Grasso, Fegato, Pancreas, Surreni, Muscoli, Cartilagine	Liquidi, Liquido cefalorachidiano, Bile, Colecisti Reni

Sequenze a sangue nero T1 pesate

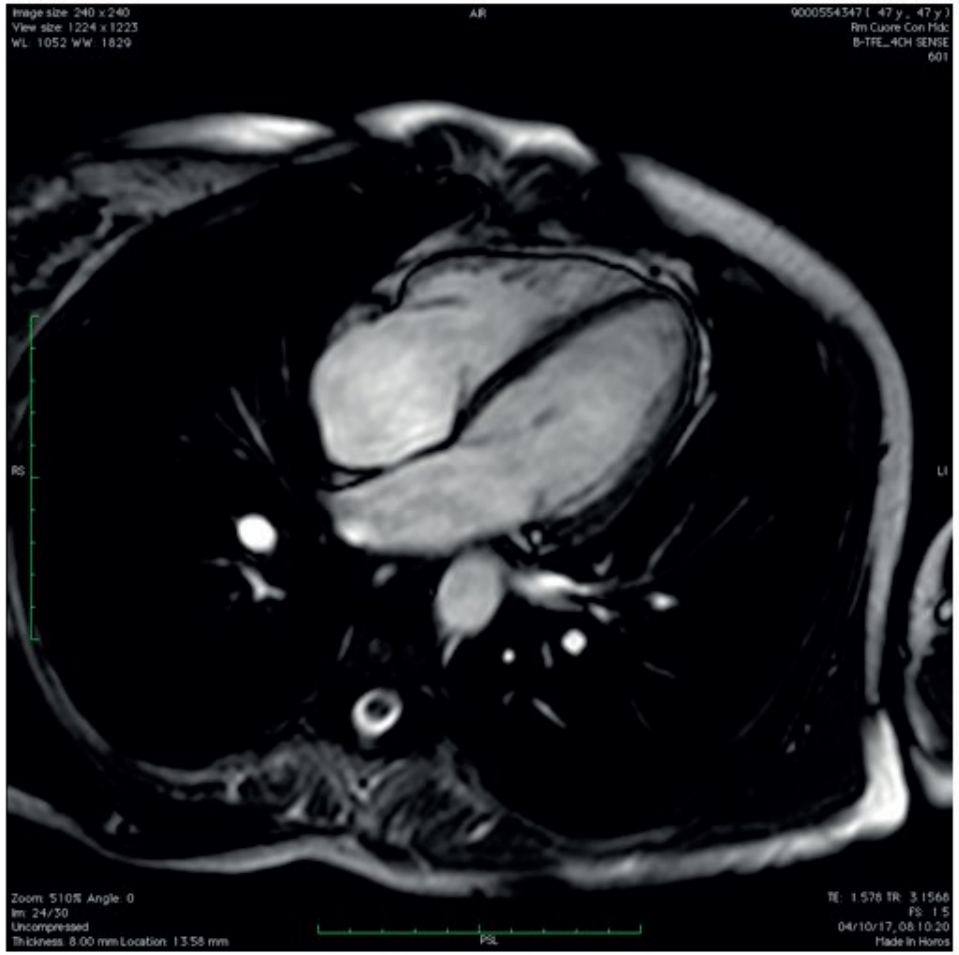


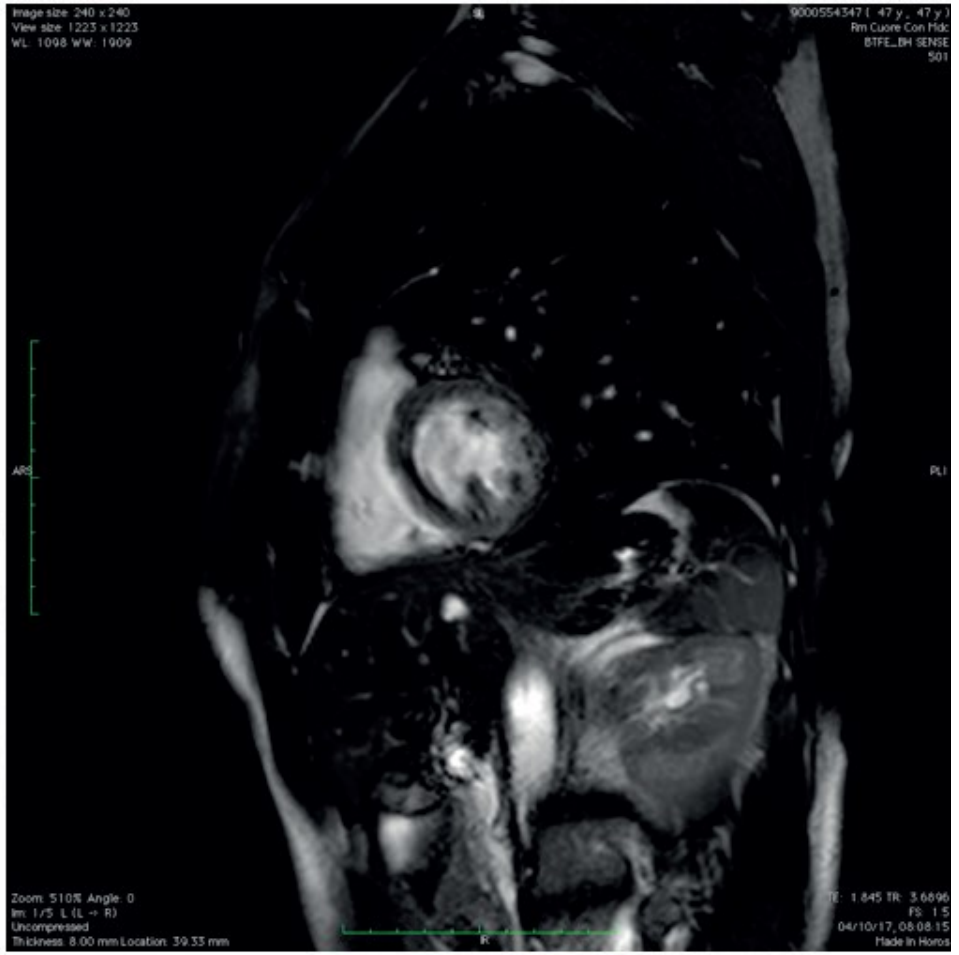
A

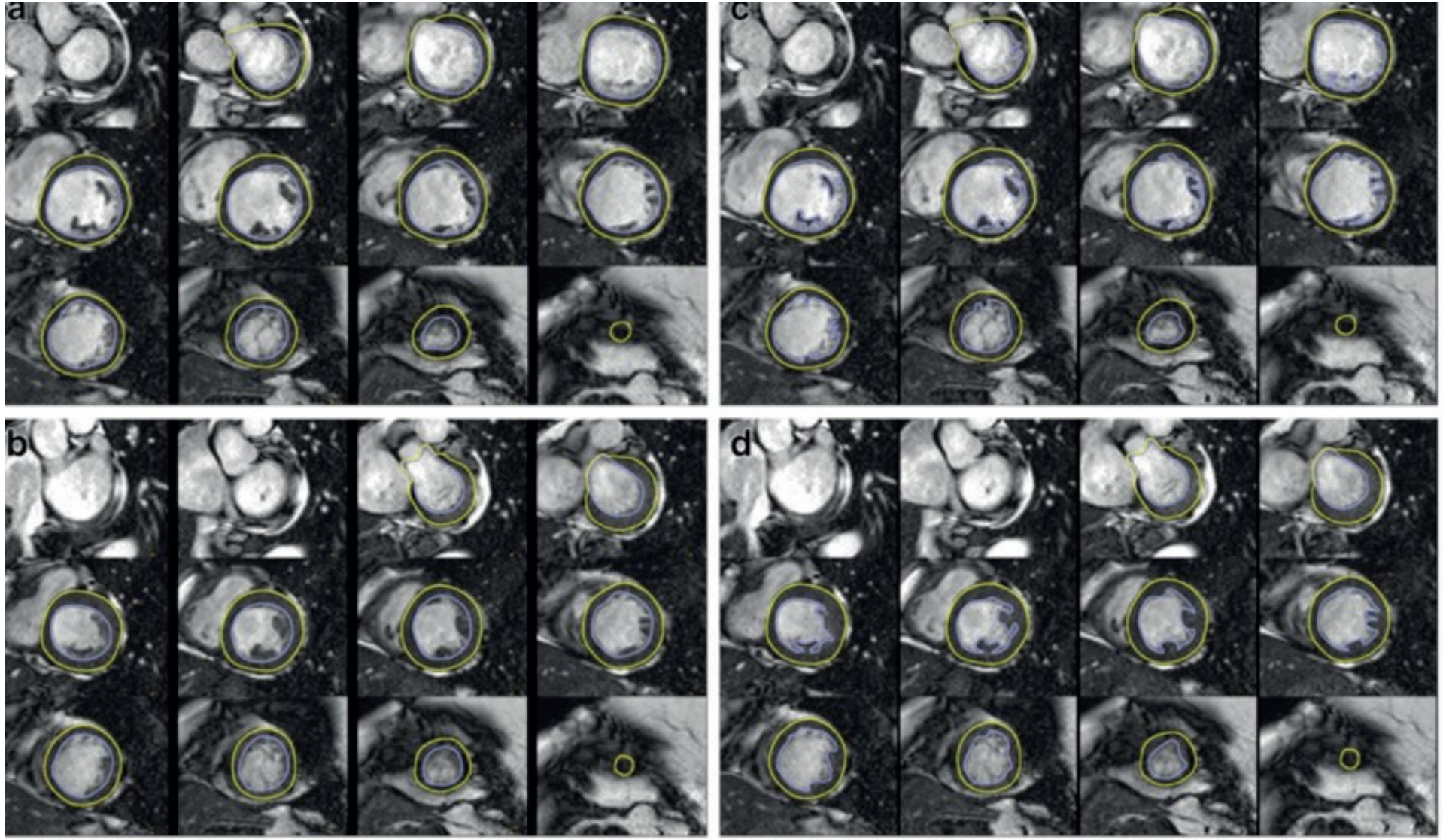


B

Sequenze a sangue bianco

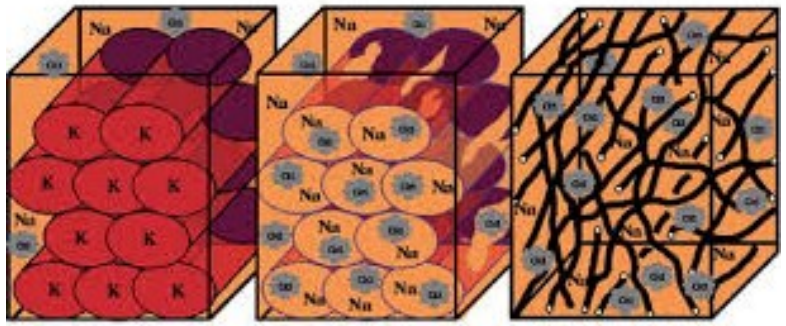




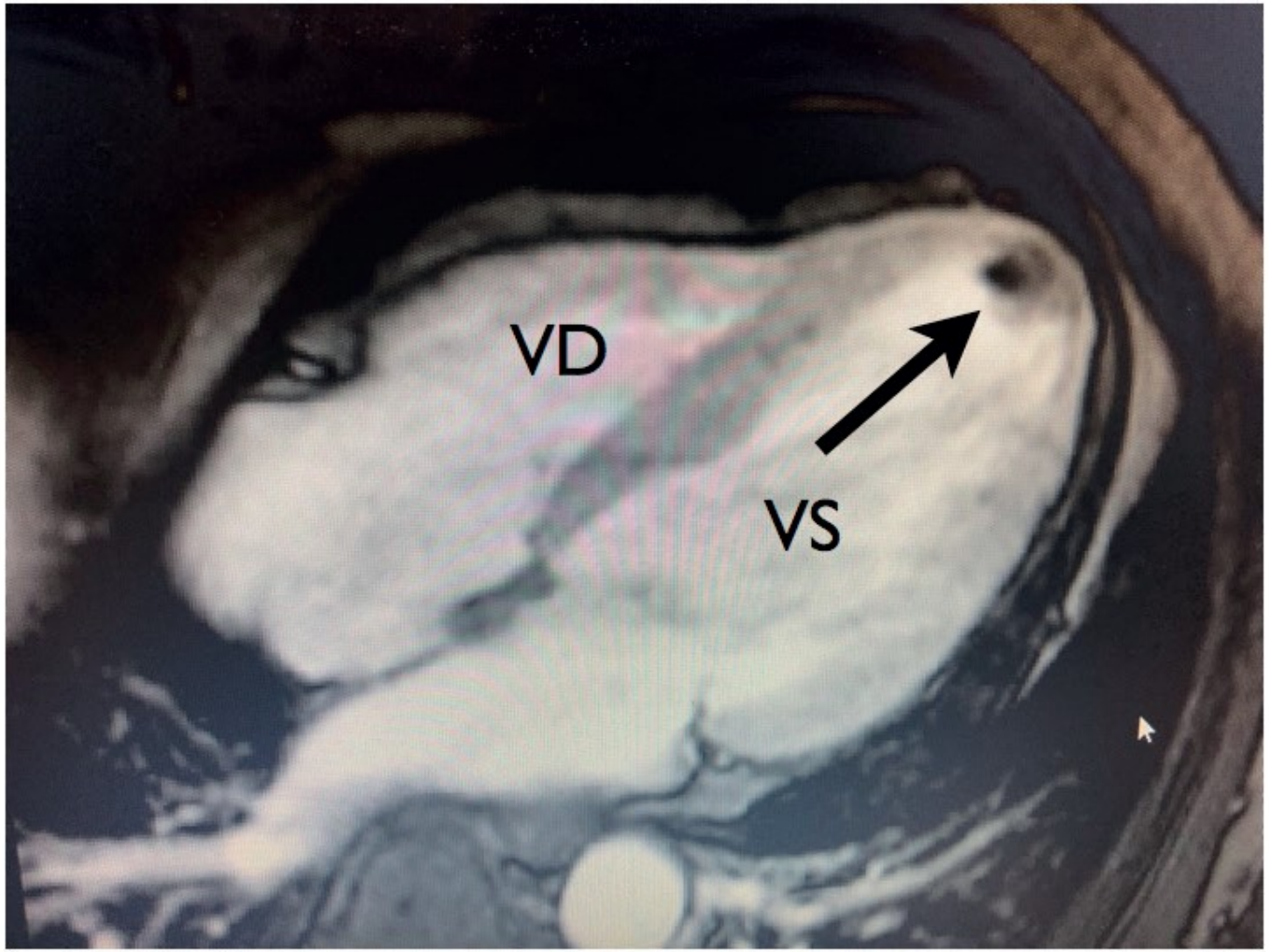

a
c
b
d

Mezzi di contrasto in RM

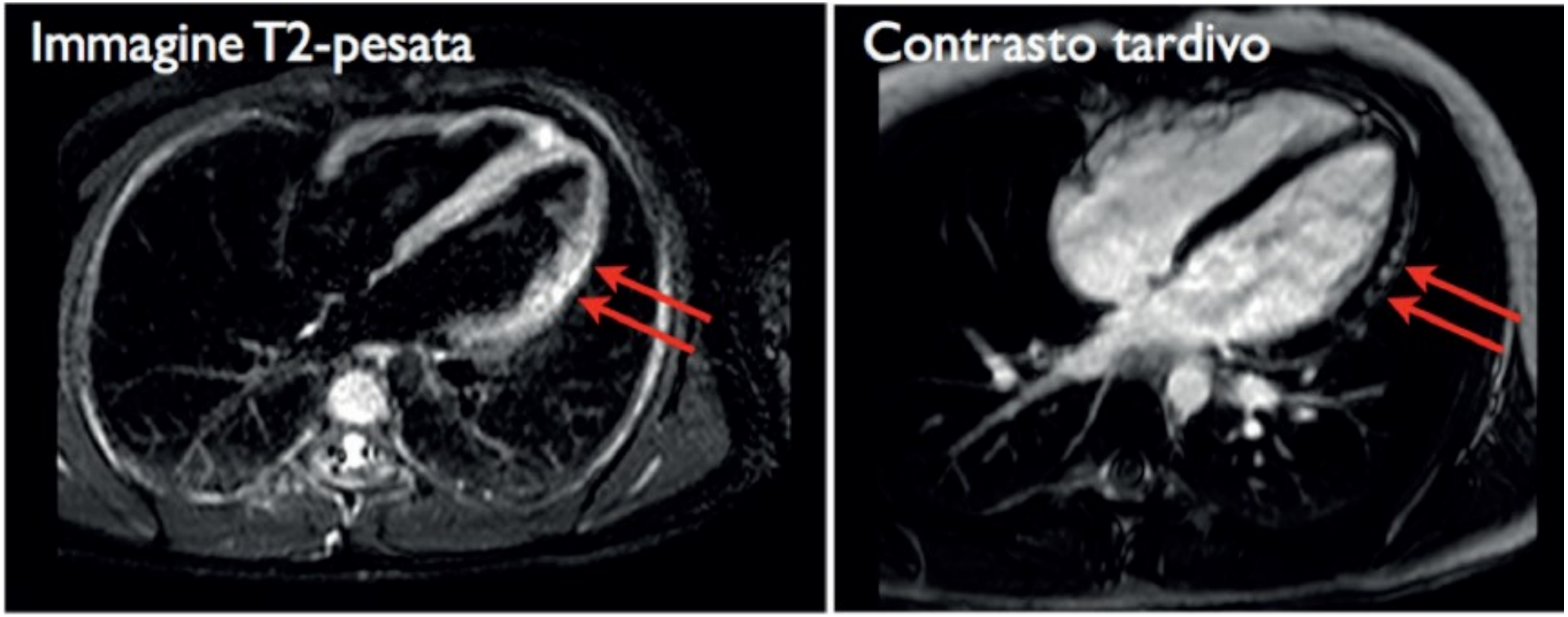
- In RM cardiaca vengono comunemente usati mezzi di contrasto a base di gadolinio, un metallo pesante a forti proprietà paramagnetiche che riduce il tempo T1 dei tessuti in cui è contenuto.
- Il gadolinio è tossico e viene somministrato sotto forma di chelati (0,1-0,2 mmol/kg).
- Il gadolinio è un mezzo di contrasto extracellulare che non è in grado di entrare nelle cellule intatte.
- Inoltre il gadolinio non trova spazio nel miocardio dove in condizioni fisiologiche lo spazio extracellulare è estremamente limitato ed il tessuto è fittamente stipato da miociti.
- In presenza di aumentato spazio extracellulare (edema, necrosi o fibrosi), il gadolinio si accumula nel tessuto e riduce il tempo T1 producendo un segnale iperintenso.



Sequenze contrastografiche precoci (EGE= Early Gadolinium Enhancement)

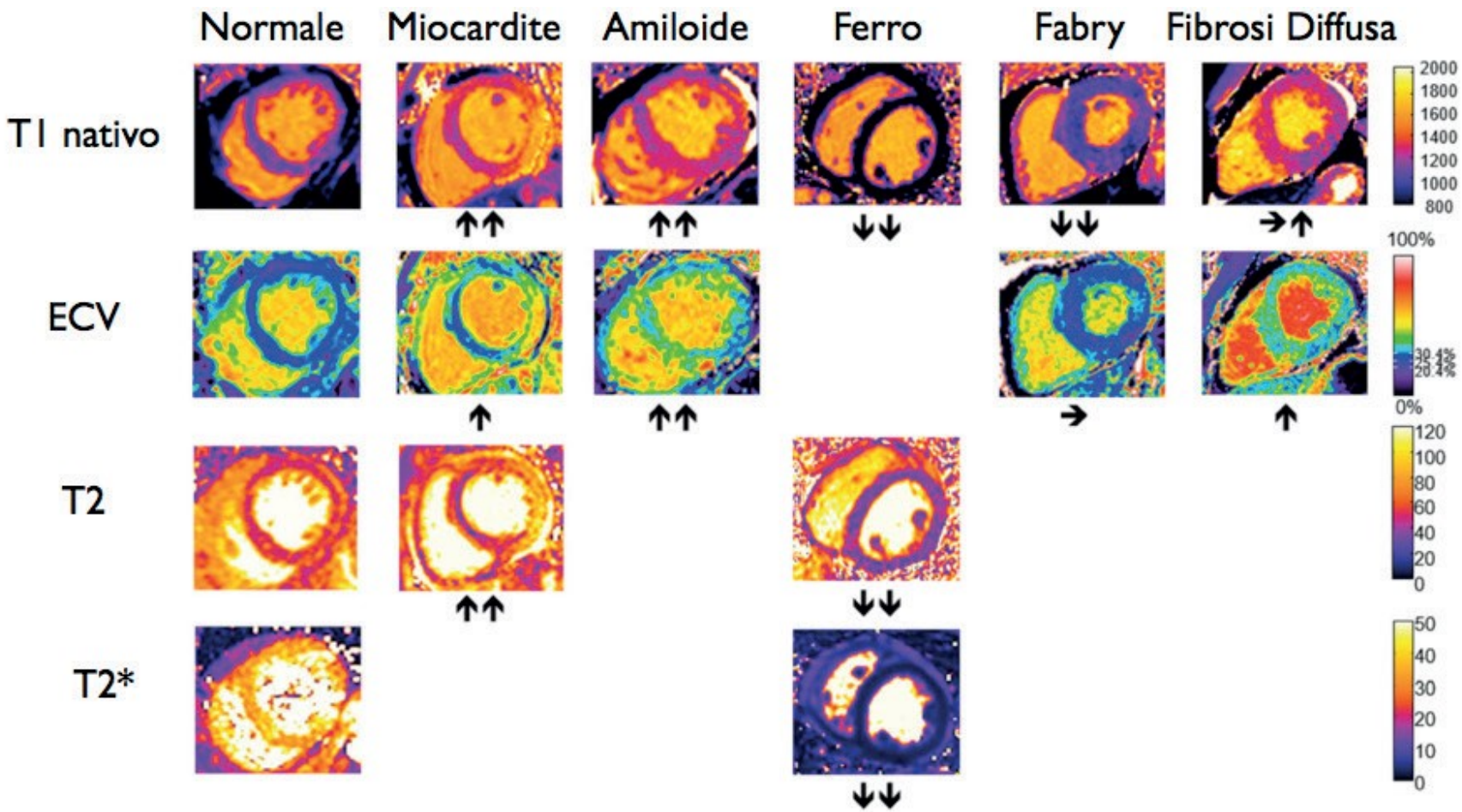


Sequenze T2-pesate e LGE

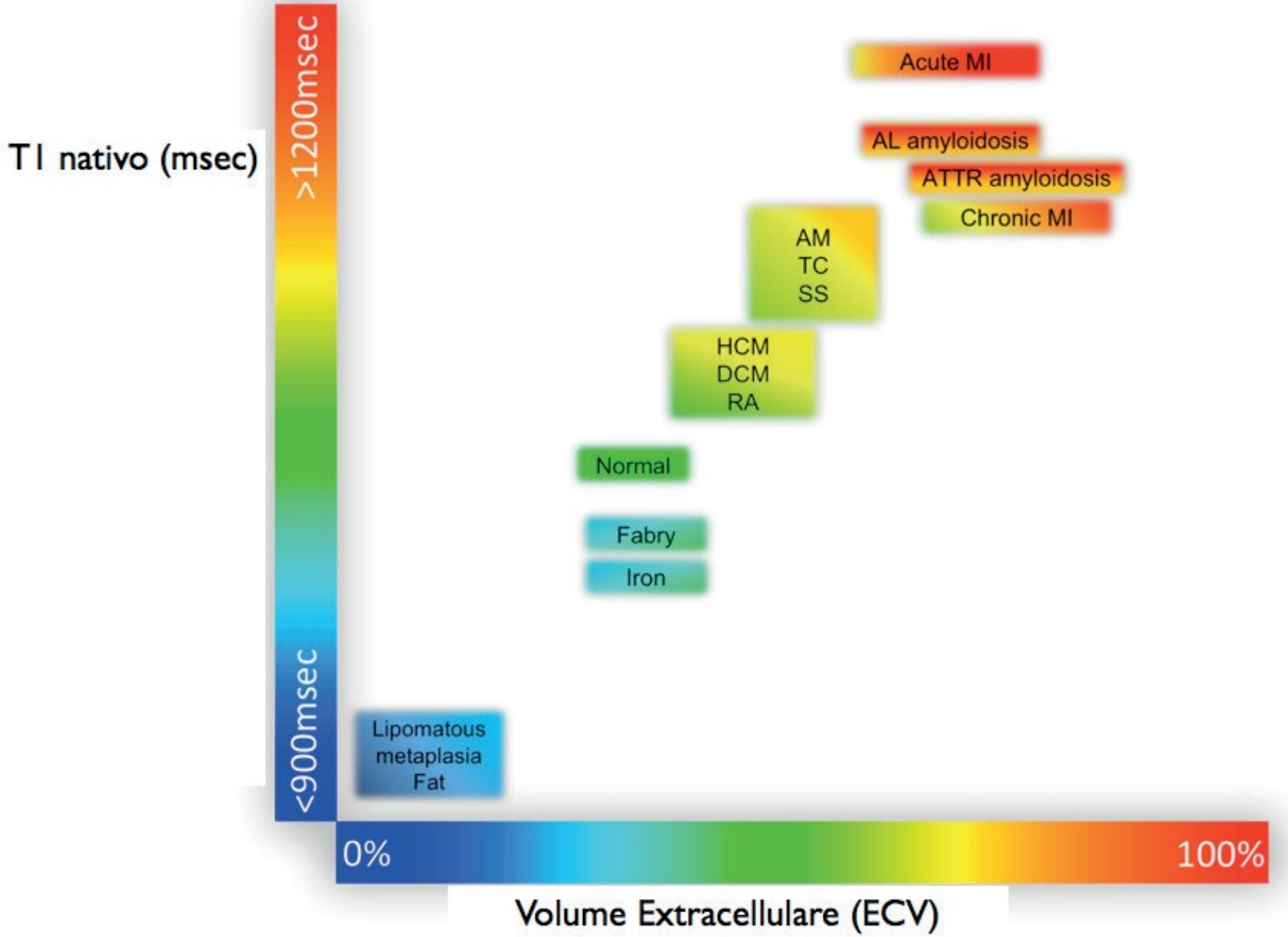


T1 e T2 mapping

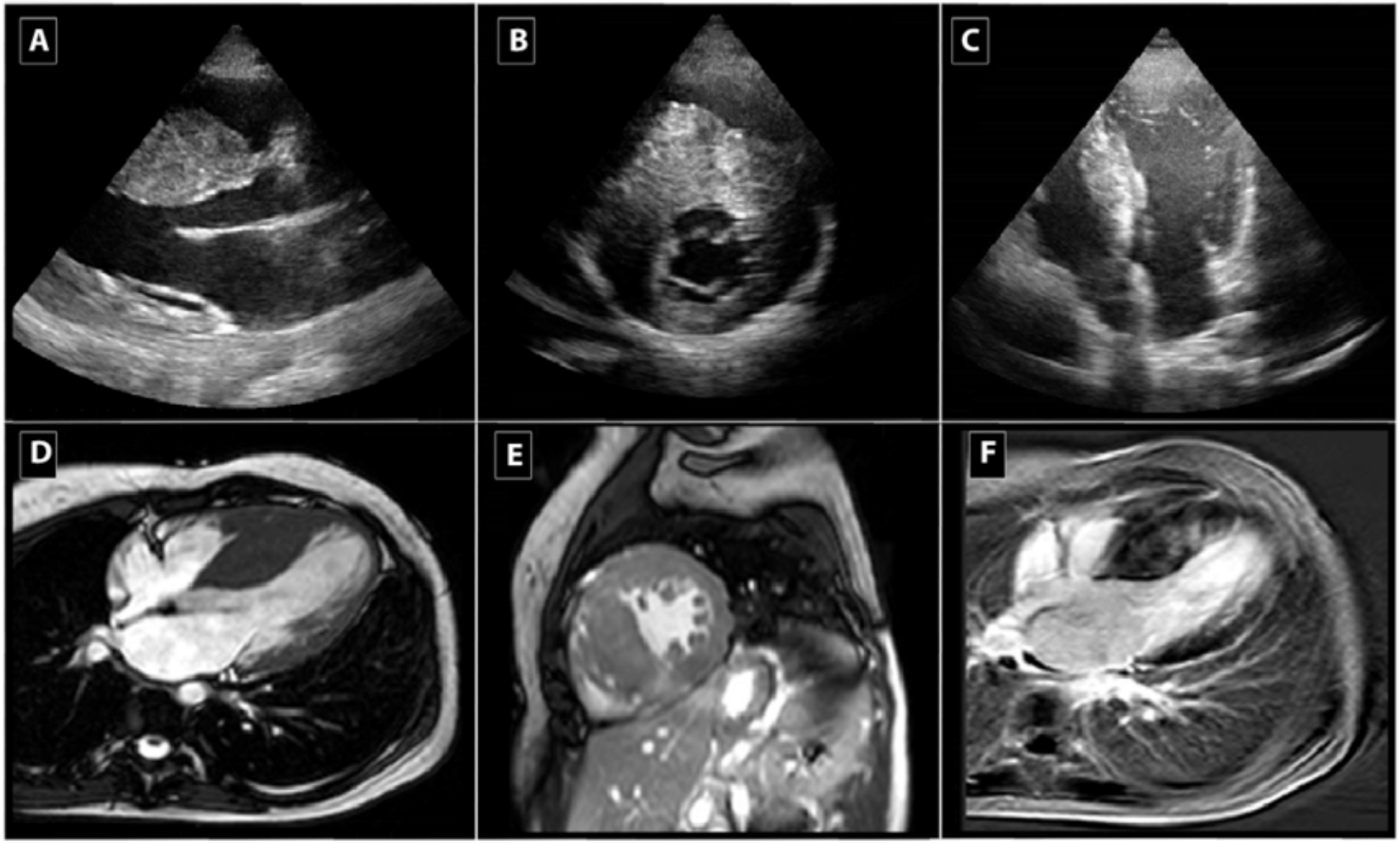
- Il mappaggio T1 consente di acquisire una mappa parametrica dove il valore di T1 è codificato in ciascun pixel.
- Il mappaggio T1 può essere eseguito prima (mappaggio T1 nativo) e dopo il mezzo di contrasto.
- Il gadolinio è un mdc extracellulare che si distribuisce in sede intravascolare ed interstiziale, ed accorcia il T1 dei tessuti.
- Il mappaggio può essere eseguito anche per T2.
- Anche in questo caso la quantificazione diretta del T2 mediante sequenze specifiche consente la costruzione di mappe parametriche, dove l'intensita del segnale esprime in termini quantitativi.


Normale
Miocardite
Amiloide
Ferro
Fabry
Fibrosi Diffusa
T1 nativo
ECV
T2
T2*
2000
1800
1600
1400
1200
1000
800
100%
30.4%
25.4%
20.4%
0%
120
100
80
60
40
20
0
50
40
30
20
10
0

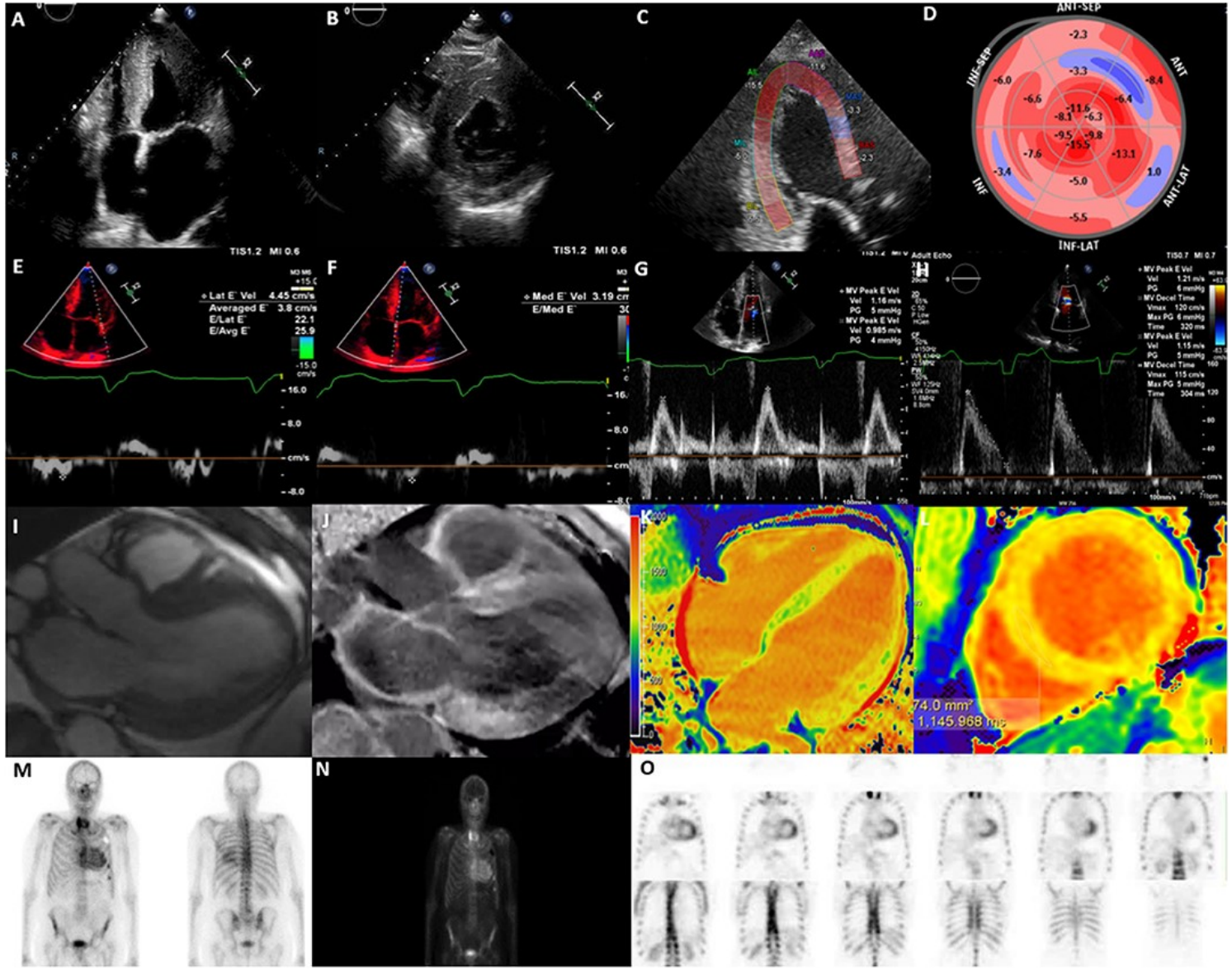
Mappaggio T1 e ECV nella pratica clinica



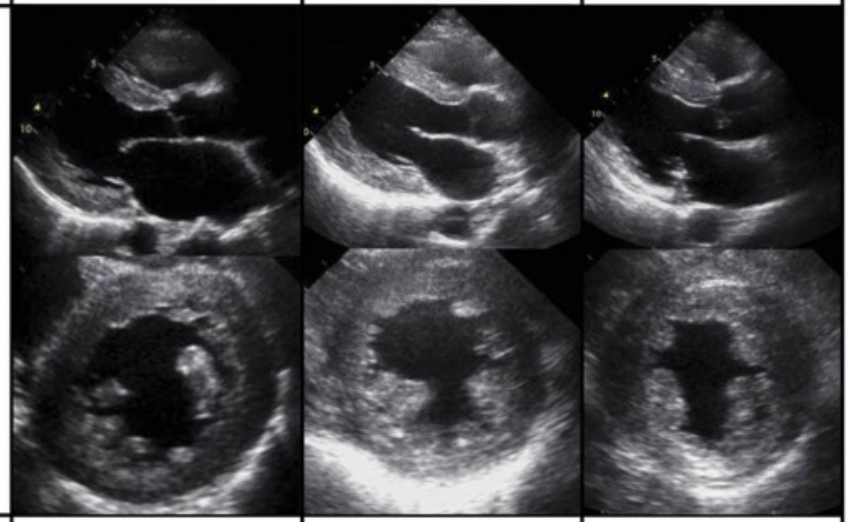
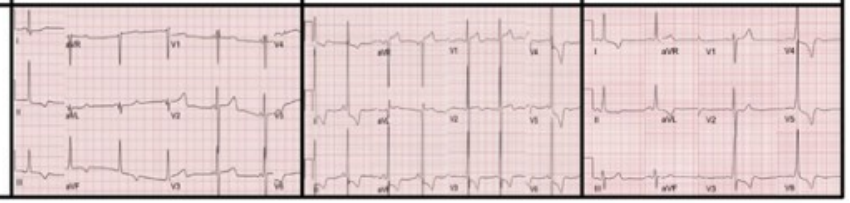
Eco e RM nella Cardiomiopatia Ipertrofica

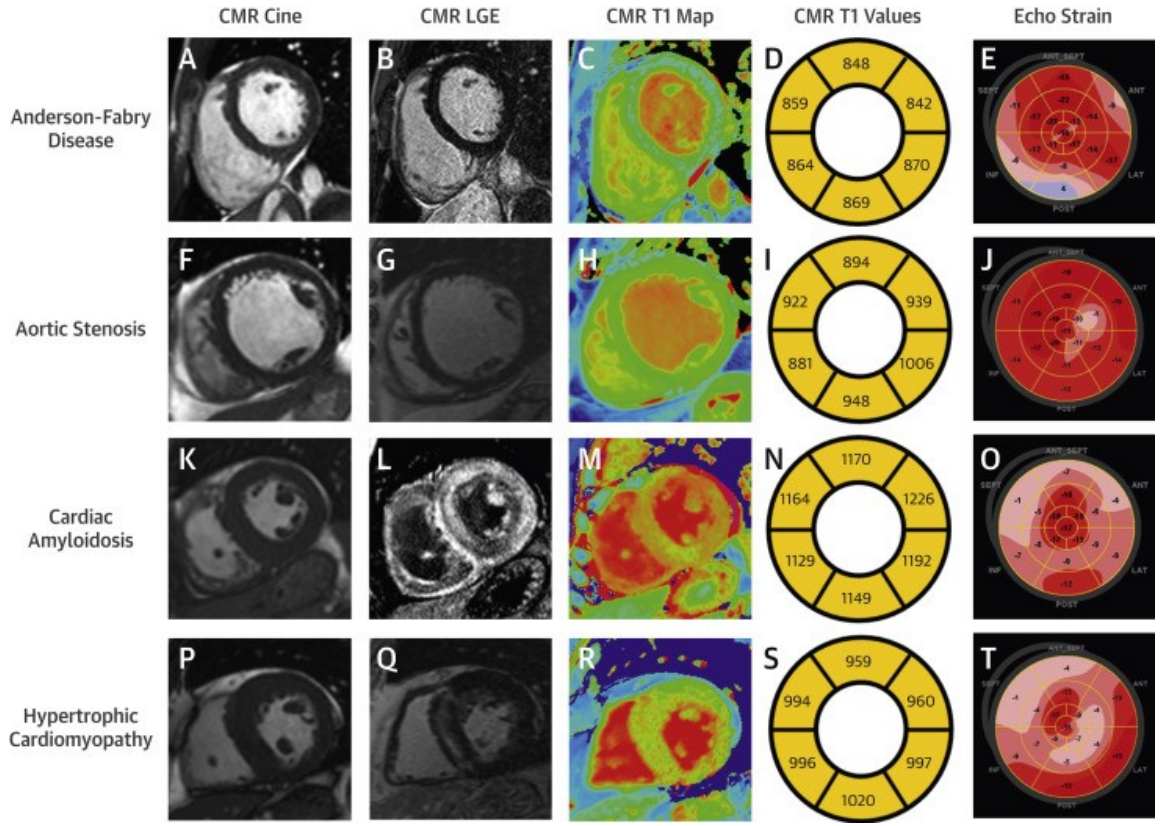


Eco e RM nell'Amiloidosi Cardiaca



ECG, Eco e RM nella Malattia di Anderson-Fabry

	Patient 1	Patient 2	Patient 3
Echocardiography			
Type of HCM (Max LV thickness)	Diffuse (16mm)	Diffuse (16mm)	ASH (23mm)
Electrocardiography			



RM cardiaca nelle cardiomiopatie

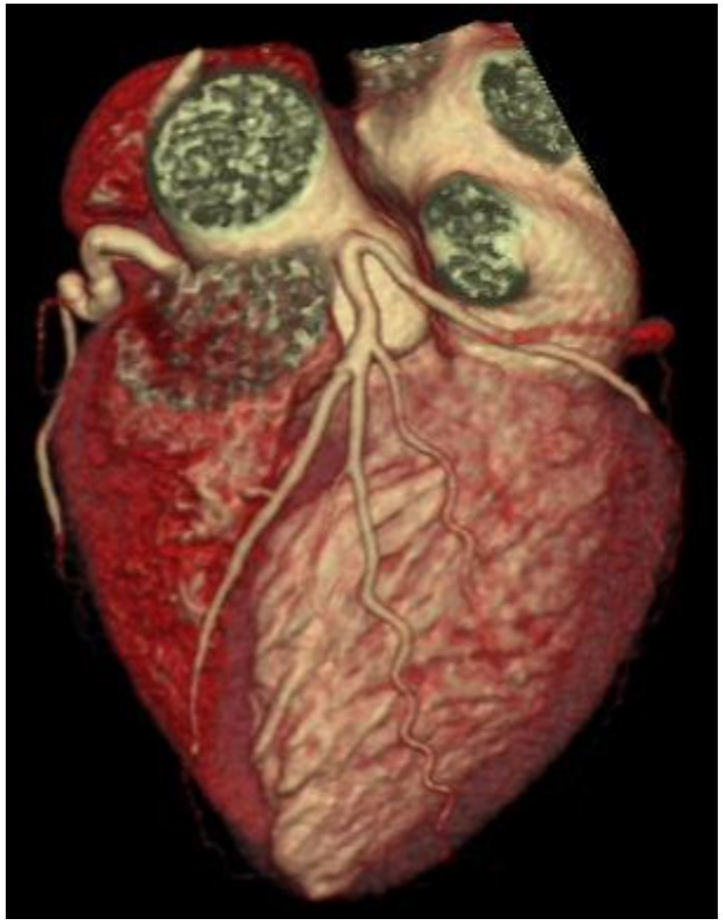
Table 7 **Cardiac magnetic resonance imaging: main hints to orient an aetiological diagnosis for each morphological phenotype**

Main phenotype	Hint	Condition to be suspected
HCM	Posterolateral LGE + Concentric LVH	Anderson–Fabry disease
	Diffuse subendocardial LGE	Amyloidosis
	Intense myocardial 'avidity' for Gadolinium	Amyloidosis
DCM	Short T2 *	Haemochromatosis
	Patchy, midwall LGE	Post-myocarditis
		Dystrophinopathy
	Akinesia/dyskinesia + LGE at the anterobasal septum or papillary muscles	Sarcoidosis
	Fatty replacement (T1w FS) within LV wall	ARVC 'Left Dominant'
ARVC	Fatty replacement (T1w FS) within LV wall	Biventricular involvement
RCM	Partial LV or RV apical obliteration + LGE at endocardial level	EMF/hypereosinophilia

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; EMF, endomyocardial fibrosis; HCM, hypertrophic cardiomyopathy; LGE, late Gadolinium hyperenhancement; LV, left ventricular; LVH, left ventricular hypertrophy; RCM, restrictive cardiomyopathy; RV, right ventricular; T1w FS, T1-weighted imaging.

TC cardiaca

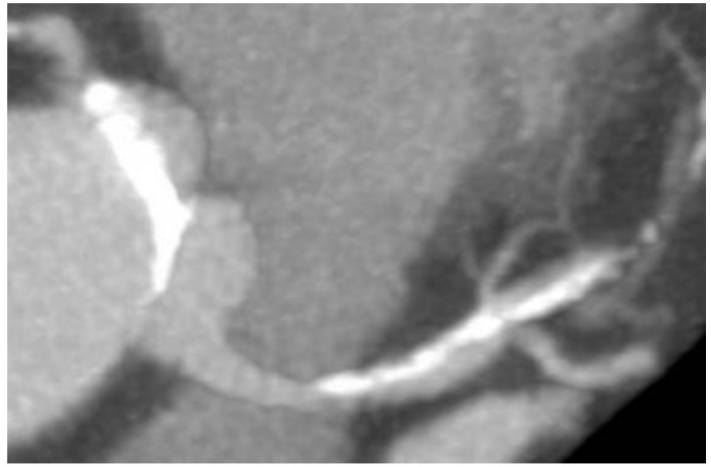
- TC a 64 strati o > (fino a 320)
- Elevata risoluzione spaziale (0,5 mm)
- Discreta risoluzione temporale (~160 ms a 64 slice)
- Sincronizzazione ECG
- Scansioni in apnea
- Velocità di scansione
- Elevata risoluzione di contrasto
- Elevata sensibilità e VPN
- Esposizione a radiazioni



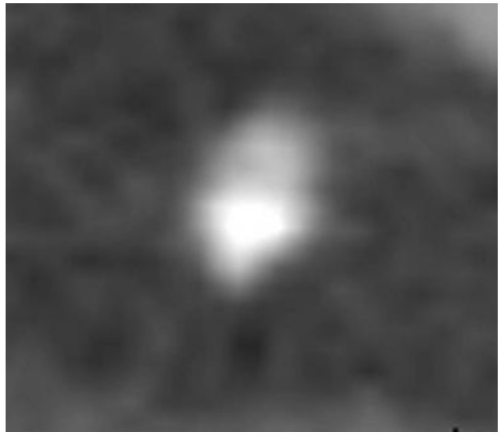
TAC Coronarica

- La **TAC coronarica** è una esame diagnostico di radiologia che permette una valutazione dettagliata dello stato di salute e la pervietà delle **coronarie**.
- Grazie alla **TAC coronarica** è possibile diagnosticare la presenza di malattia **coronarica** e individuare le anomalie anatomiche delle arterie **coronarie**.

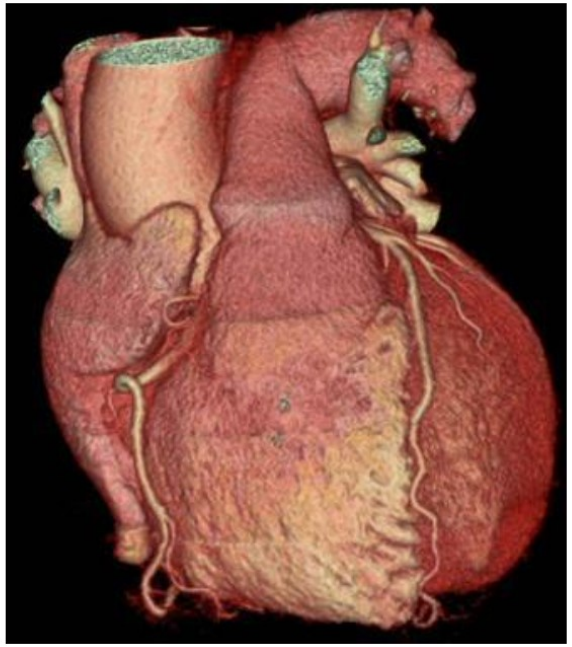
Imaging cardiaco con TC

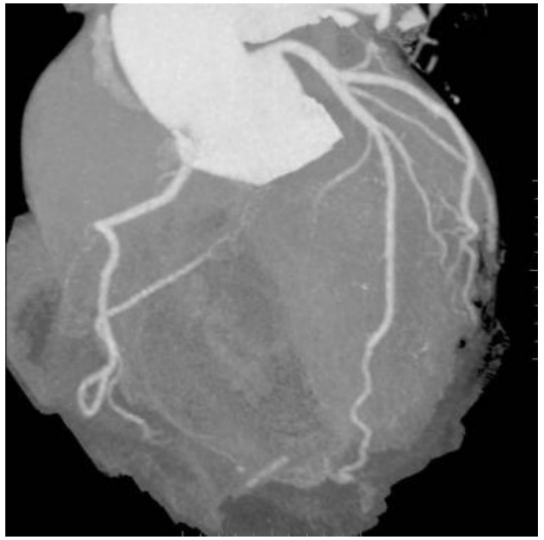


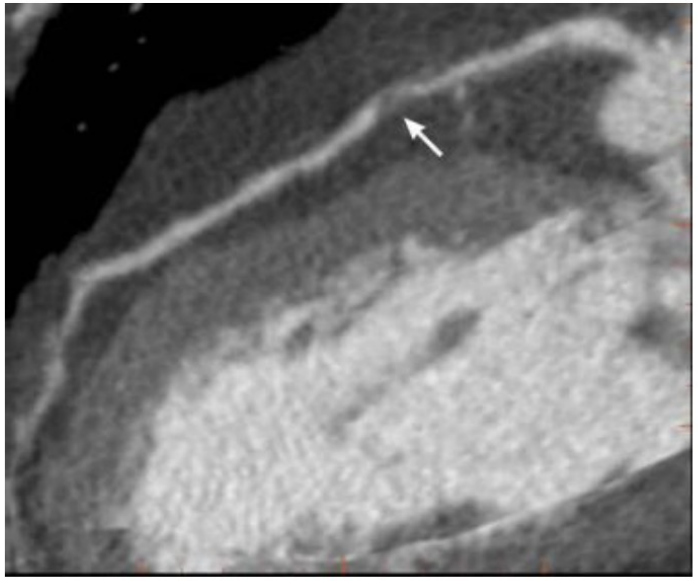
MIP: maximum intensity projection



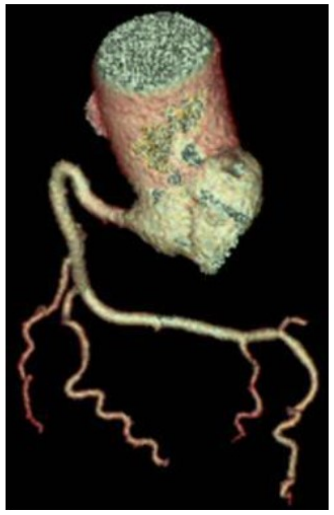
MPR: multiplanar reconstruction





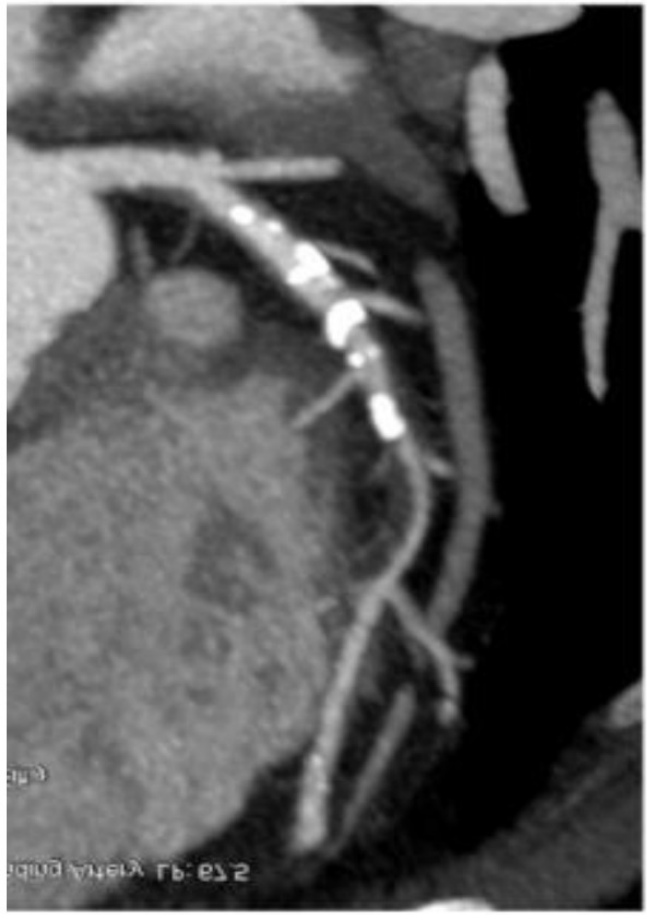


3D rendering

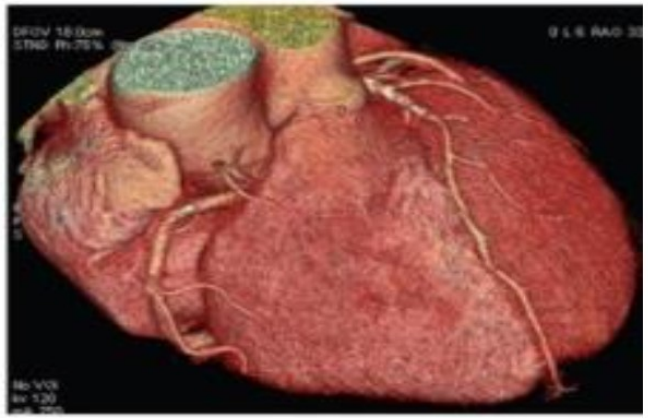


Imaging coronarico con TC

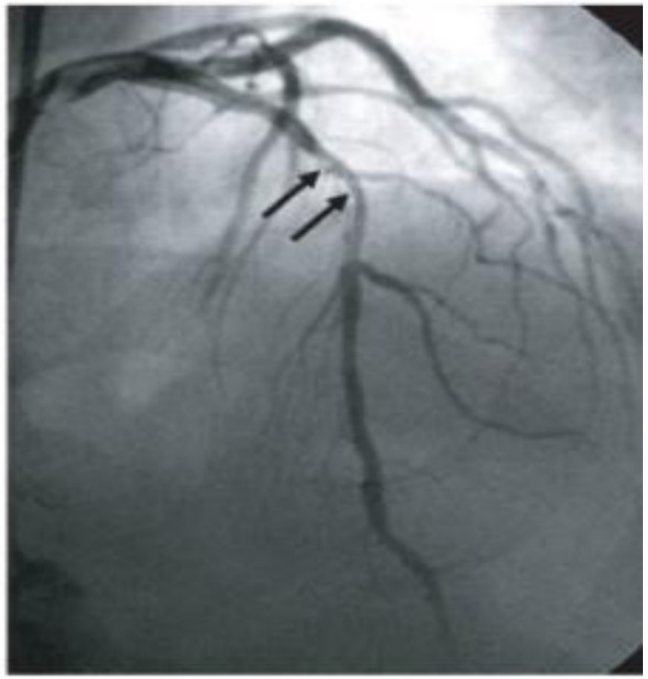
Placche calcifiche su IVA



(c)



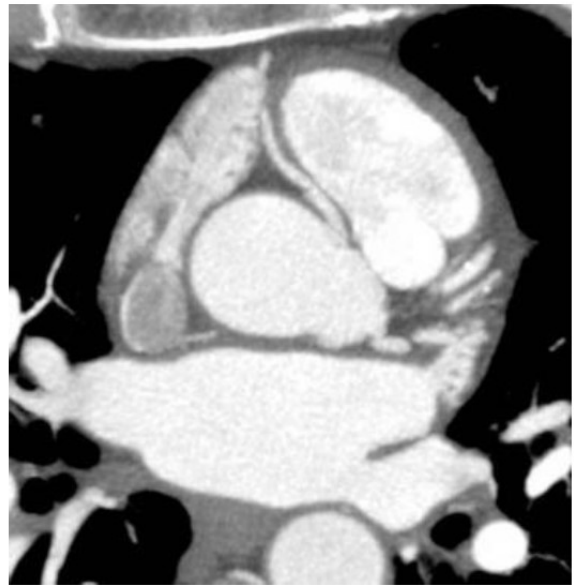
(d)

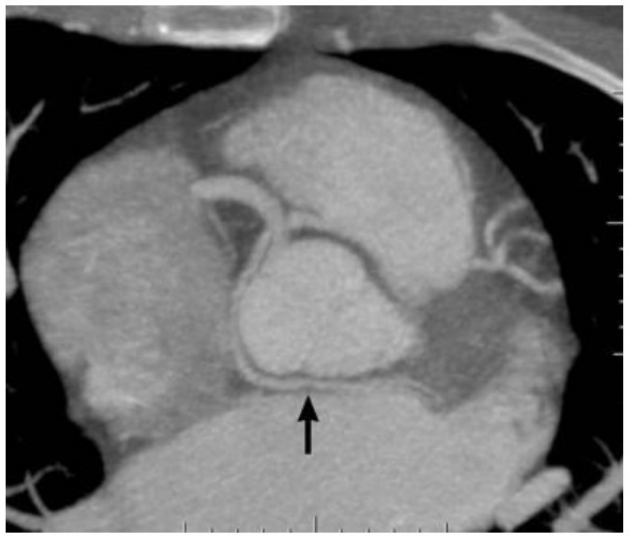


(e)

Cardiopatie congenite

- Diagnosi e valutazione pre-operatoria, anche in urgenza clinica
- Esame molto rapido, blanda sedazione
- Esposizione radiazioni (bambini)
- Anomalie extra-cardiache associate
- Anomalie coronariche
- Coartazione aortica e anomalie arco
- Studio collaterali sistemico-polmonari
- Valutazione e follow up di stent polmonari, spirali metalliche, homograft…





Cardiac imaging modalities

Modality	Underlying principle	Primary attributes	Key uses
Echocardiography	Analysis of reflected ultrasound waves at tissue interfaces	High frame rate, high spatial resolution, very high temporal potentially (e.g. Doppler) bedside, safe	Cardiac structure and function. Valve structure and function. Identification of ischaemia and viability (stress echo)
Magnetic resonance imaging	Electromagnetic waves emitted from protons in response to a pulsatile magnetic field	Tissue characterization Spatial resolution. Safety	Cardiac muscle and chamber structure function; tissue characterization, ischaemia (metabolism)
CT imaging	Differential absorption of X-rays	Cardiac structure including coronary arteries; high spatial resolution	Cardiac including valve structure and coronary circulation. FFR
Nuclear Imaging (including combined with CT/CMR)	Uptake and wash out of radio tracers (gamma emitting or positron emitting)	Functional assessment of myocardial perfusion, metabolism, innervation and vascular inflammation. Possible quantitation and integration	Detection of myocardial ischaemia, viability, and denervation. Detection of infection

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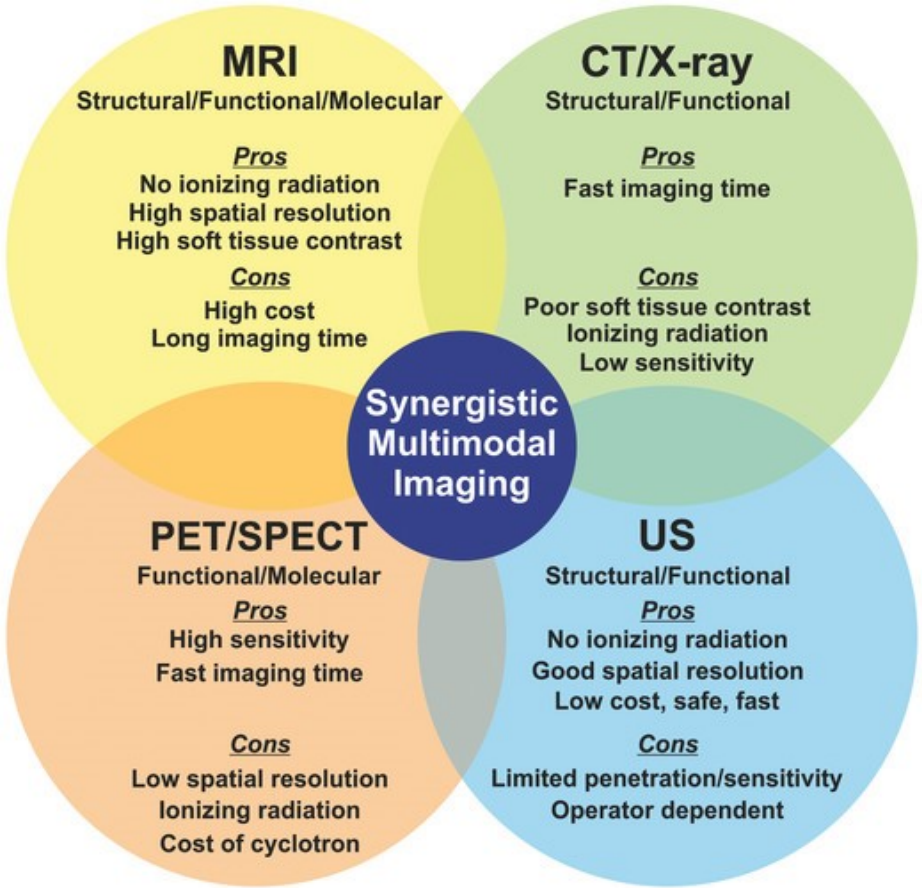
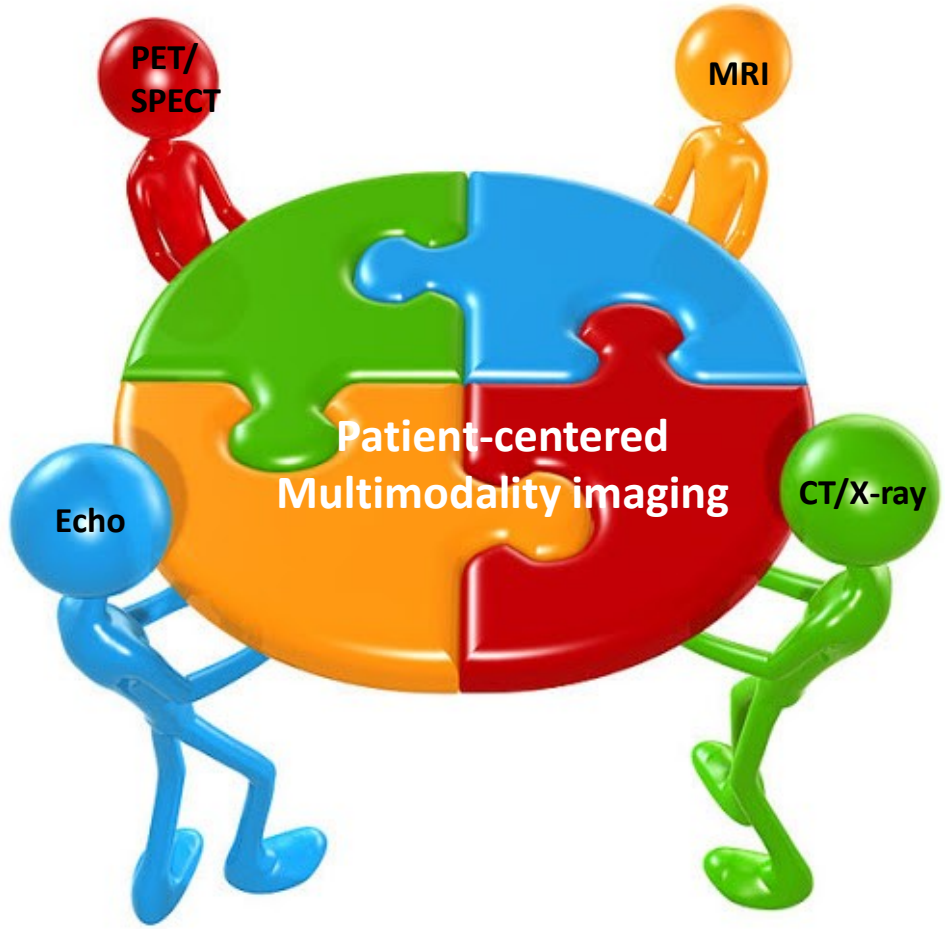

MRI
Structural/Functional/Molecular
Pros
No ionizing radiation
High spatial resolution
High soft tissue contrast
Cons
High cost
Long imaging time
CT/X-ray
Structural/Functional
Pros
Fast imaging time
Cons
Poor soft tissue contrast
Ionizing radiation
Low sensitivity
Synergistic Multimodal Imaging
PET/SPECT
Functional/Molecular
Pros
High sensitivity
Fast imaging time
Cons
Low spatial resolution
Ionizing radiation
Cost of cyclotron
US
Structural/Functional
Pros
No ionizing radiation
Good spatial resolution
Low cost, safe, fast
Cons
Limited penetration/sensitivity
Operator dependent


PET/ SPECT
MRI
Patient-centered Multimodality imaging
Echo
CT/X-ray

UDINE-Piazza della Libertà

Grazie per la Vostra attenzione!