Clinical Arrhythmology

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Second Edition

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Foreword by Dr. Valentin Fuster

When I received the manuscript from Antoni Bayés de Luna and his collaborators to write a foreword for this book, I realized at a glance what a great opportunity this work provides. This has been the rule with books published by Antoni Bayés de Luna – they appear when they are needed most. I still remember his book on electrocardiology, which explained the technique of "Electrocardiography" for beginners in a way that was not only concise but very thorough. This book has been translated into eight languages and remains very successful throughout the world. This also occurred with his book on "Sudden death", as well as his correlations between electrocardiography and cardiovascular magnetic resonance imaging. But for now I would like to talk about *Clinical Arrhythmology*, which is what interests us most. The current books on arrhythmias mainly explain the great technological advances being achieved in diagnosis and, in particular, the interventionist treatment of cardiac arrhythmias. However, most of these books fail to examine the clinical aspects closely enough and do not emphasize the crucial role in diagnosis of the surface electrocardiogram, nor do they discuss how the clinical cardiologist or family doctor, or even the emergency medicine doctor, might proceed once this diagnosis is performed, in order to rapidly and efficiently treat the specific arrhythmias in the clinical context in which they appear. The book is full of the experience of Antoni Bayés de Luna teaching electrocardiology and arrhythmias in the style of Paul Puech, Leo Schamroth, and Charles Fisch, with an updated state-of-the-art view of the management of arrhythmias.

This book is filled with advice on how to diagnose and effectively treat arrhythmias with classic knowledge that, at the same time, is up-to-date, using many references from 2010. Antoni Bayés de Luna emphasizes the necessity to consult and use the medical guidelines of the scientific societies, while at the same time giving a personal touch derived from his considerable experience. This is especially present in Chapter 1, where he emphasizes the importance that history taking and physical examination still have when diagnosing and treating arrhythmias. He gives a series of recommendations that state the necessity to know heart anatomy and physiology well, in addition to outlining how to approach a case with arrhythmias. I also consider the updated physiopathologic mechanisms of arrhythmias to be of great interest. Later on, in the second part of the book, all the different clinical, electrocardiographic, prognostic, and management aspects of different arrhythmias are clearly commented on. The third part deserves close study because it is where sudden death, being the most important complication of arrhythmia, is examined and discussed in different heart diseases and situations.

I feel that this book demonstrates the great authority of the author, as well as his deep knowledge of clinical arrhythmia and electrocardiography, great didactic capabilities, and many years of experience in this field. I am sure it will be extremely useful for doctors who are first faced with cardiac arrhythmias, not only in the diagnosis but also in obtaining a clear idea on how to focus management of the condition, including the last advances in the treatment through ablation techniques and pacemaker and defibrillator implantation in different types of arrhythmias.

I would like to offer my wholehearted congratulations to Antoni Bayés de Luna for providing all his personal experience in a subject of great clinical importance and based on the crucial value placed on the history taking and, especially, the surface electrocardiogram in the diagnosis and management of cardiac arrhythmias.

I predict that this book will be a huge success because of its usefulness and timeliness. It will make diagnosis and treatment of different cardiac arrhythmias much easier for students, doctors, and even specialists, without the apprehension often generated in the medical community.

Dr. Valentin Fuster
Director, Mount Sinai Heart Center, New York
Professor of Medicine, Mount Sinai School of Medicine
Past President, American Heart Association
Past President, World Heart Federation

Foreword by Dr. Pere Brugada i Terradellas

When Professor Antoni Bayés de Luna placed 3 kg of printed material in my hands, I immediately knew what was happening: the "master of masters" had struck again. Undoubtedly, it was a new book. And, undoubtedly, it was a book related to electrocardiology, the great love of his life. Knowing him as I have for so many decades, I did not doubt that the manuscript I was now holding had been written to fill a gap in medical knowledge. But what could Antoni have written now that he had not already written? His various books on electrocardiography, published in the most common languages, are known by every admirer of the electrical activity of the heart. No cardiologist has described the electrocardiogram in as much detail as he. His daily work has consisted of the nearly impossible job of dissecting the electrical activity of the heart. And this all without electrocuting himself!

I looked carefully at the title on the first page and those 3 kg soon became lighter: *Clinical Arrhythmology*. Here was the big secret. Finally, the book that describes the mechanisms, diagnostic clues, and management of cardiac arrhythmias, written by the clinical cardiologist for the clinical cardiologist. Thanks to great advances in the study of cardiac electrophysiology, arrhythmia mechanisms are well understood today. However, the general cardiologist, the internist, and the general practitioner must depend continuously on the electrocardiogram to define the swelling mechanism in any cardiac rhythm disorder. Combining clinical and electrophysiologic knowledge with an updated approach of medical management, to produce an integrated textbook of clinical arrhythmology is a challenge few would take on. For this, a clinical and scientific tenacity is required that only a chosen few possess, one of whom is Professor Antoni Bayés de Luna.

These thoughts crossed my mind during the minutes I took to look through the manuscript. Antoni, aware of my love for his work, asked if I would like to write a foreword for this book. Absolutely! I said, I would do it with great pleasure, in order to thank him on behalf of myself and many others for his great efforts in teaching, and for the numerous hours of pleasant reading he has given us. To thank him for the great care he has always taken with his books, including this one, naturally, to offer us clear outlines accompanied by greatly didactic diagrams, which are a pleasure to read and study.

Clinical Arrhythmology is obligatory reading for any physician directly or indirectly related to disorders of cardiac rhythm, including cardiologists, internists, sports medicine doctors, and general practitioners. They will find in this book that a combination of clinical experience and great electrocardiographic skills is the best way to approach successfully the diagnosis and treatment of cardiac arrhythmias. It is also a superb resource for paramedics who may be faced with cardiac arrhythmias.

Professor Bayés de Luna must be congratulated on his magnificent effort and the excellent end result of this book.

Dr. Pere Brugada i Terradellas
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Preface

A few years ago, I, Antoni Bayés de Luna, wrote a book on *Clinical Arrhythmology*. The title was chosen to express that my aim was to share with the reader my point of view, as a clinical cardiologist, of what are the most important concepts related to arrhythmias, including genetic, epidemiological, and diagnostic aspects that may be useful to treat these patients. My objective was to ensure that the clinician who is facing a patient with a possible or already established arrhythmia has gained, after reading the book, all the information necessary to diagnose arrhythmias, understand ECG tracings, and obtain a good clinical history. I also aimed to teach about the prognosis of certain conditions, including the risk of possible complications such as stroke, cognitive impairment, and sudden death, so that the clinician could decide what the most appropriate treatment is.

In order to reach this goal, the book is divided into three sections.

In the first section, the concept, classification, and clinical aspects of arrhythmias are presented, with emphasis on its relation to sudden death, as well as the most interesting information still relevant today on the great utility of anamnesis and physical examination. The characteristics of each type of cardiac cell are described and, finally, the most important electrophysiological mechanisms associated with cardiac arrhythmias are also discussed.

The second section describes the key elements used to carry out an electrocardiographic diagnosis of the various active and passive arrhythmias, their clinical and prognostic implications, and the best available treatments, using a practical approach. The current use of antiarrhythmic agents and the various techniques (cardioversion and ablation) and implantable devices (pacemakers, defibrillators, etc.) available are also briefly discussed (these topics are discussed more extensively in the Appendix).

In Chapter 7, the reader will find out how to perform an analytical study and differential diagnosis of different arrhythmias.

The third section deals with the most frequent arrhythmological syndromes, including pre-excitation and channelopathies, as well as other electrocardiographic patterns suggestive of increased risk of sudden death.

Finally, in the Appendix, a few concepts that are necessary to understand the literature are expanded on: sensitivity, specificity, and predictive values. In this section, new antiarrhythmic agents and novel techniques for diagnosis and treatment are covered. Guidelines issued by the most important scientific societies are also mentioned.

Throughout the book, emphasis is placed on the importance of surface electrocardiography as the basic technique to diagnose arrhythmias at a clinical physician's level.

All the information is presented in a cohesive way, although at times it may result in repetition of some aspects and concepts. I am aware of this, but believe it to be useful, particularly to the nonexpert, in order to reinforce basic knowledge and ideas. At the same time, the reader is very often referred to further information, either by cross-references related to other sections of the book or by reference to sections just before ("see before") or after ("see after") in the same chapter. I believe that this makes the book more harmonious and allows to the reader to interact better with other parts of the book. Additionally, at the end of each chapter, there are self-evaluation questions, the answers to which may be found on the pages of the book where the corresponding "letter tag" appears in the margin.

In terms of bibliography, a list of updated recommended texts for general reference is provided after this preface. In addition, at the end of each chapter, there is a list of specific references pertaining to each particular subject. The name of the first author of each of these articles has been cited in the text in an appropriate position.

I am sure, therefore, that after reading this book the reader will have learned all the basic concepts needed to face the often difficult problems of immediate diagnosis based on electrocardiographic tracings. I hope the reader will not only understand the most important clinical, prognostic, and therapeutic implications of the diagnosis

in every case but also will acquire more confidence in this task.

This book is the result of many years of teaching cardiology, especially electrocardiography and arrhythmias. It is a source of pride for me to have Valentin Fuster and Pedro Brugada, two of the greatest representatives of cardiology in the world on both sides of the Atlantic, Catalans like me and good friends of mine since the beginning of time, honor me by writing glowing forewords for the book. I feel that their words not only complement the work but also express its meaning for the general cardiologists, cardiology residents, and internists.

I am very pleased that the book was very well received by general practitioners and clinical cardiologists, and when the Publisher decided to produce a second edition I suggested that an update of all the information given in the text, especially in relation to diagnostic criteria, new types of drugs and devices, and new prognostic implications, was needed. It was also very important to provide an update on new electrophysiological techniques, such as all types of pacemaker, new Holter devices, ICDs, CRT, and, especially, ablation techniques, including the new devices for LAA closure, and so on. This update had to be not only related to the technical aspects of the procedures but especially devoted to a discussion of when each technique should be indicated and the most characteristic aspects of each one of them.

In order to help this book evolve into a classic "*Textbook of Clinical Arrhythmology*", we decided that it was necessary for the new edition, and especially for future editions, to incorporate a co-author who would bring a new flavor but maintain the philosophy of a *book of one author* (not a book written by many authors each with different points of view and one editor-in-chief). This was for me a crucial point.

In order to do this, we decided to invite Professor Adrian Baranchuk, Head of the Heart Rhythm Service from Queen's University, Kingston, Ontario, Canada, to become a co-editor of the book. Adrian has demonstrated to me all the requirements that I have explained before: he is a very good clinician and an excellent and up-to-date invasive electrophysiologist, with a great teaching vocation and an extraordinary capacity to transmit knowledge. Therefore, he was for me the best person to transform a second edition of the book into an updated one that includes all the new aspects of our profession developed during the last five years whilst simultaneously maintaining all the characteristics of an authoritative author book. I have worked with him in different projects for the last few years and I was very confident that he has, without any doubt, the adequate scientific profile to perform this task.

I hope that the scientific community will receive the book enthusiastically as a "textbook" for cardiology fellows, internal medicine and emergency residents, medical students, general practitioners and allied professionals.

Lastly, I thank very much all the collaborators that have contributed to the first edition and that continue to contribute in this second edition. I also welcome the new contributors to this second edition. Additionally, thanks very much to our mentors and many other collaborators that have supported us in many aspects. Great appreciation must be shown to the amazing secretarial support from our beloved Montse Saurí and Esther Gregoris, and especially to my family, my wife María Clara for her constant support and all my five children and their families.

Preface to the Second Edition by Dr Adrian Branchuk

Now, I will introduce Adrian Baranchuk to write the second part of this foreword.

It is certainly not "common place" when an opportunity arises like the one Professor Bayés de Luna has given me to join him as co-author of the second edition of *Clinical Arrhythmology*. I am thrilled, honored, and challenged by this offer. I have carried out all my medical education in Argentina, reading from Professor Bayés de Luna's books and listening to him delivering talks and teaching large audiences all around the world. To me, he represents all that I wanted to achieve in my academic career. I still cannot believe that I have the opportunity to discuss electrocardiography, arrhythmias, and cardiovascular diseases with him. Dr Bayés de Luna is a super active physician, an avid researcher, and a spectacular mentor.

When he invited me to co-author this amazing book (the first edition of which I had on my shelf), I accepted immediately without knowing what I was getting into.

I have read and revised each line of this incredible treasure. There is so much to learn from this book!

He asked me to look at it with my "young eyes" (he called it "young blood") to be sure that we were not missing any new relevant information. I did my best to accommodate summaries of all new techniques, both for diagnosis and treatment. I am sure that I have missed a few important issues, and I hope we will correct these omissions in the next edition.

The last five years of my career have been enlightened by the constant presence of Professor Bayés de Luna. His advice both in the areas of academic medicine and also in more personal aspects of my life, have produced a change in how I face medicine, and how I balance my academic career and my personal life. For that, I will always be grateful and I hope to be able to transmit the same "spirit" to my students.

Clinical Arrhythmology is a book for anyone interested in clinical arrhythmias and electrocardiology. It is written

in the very special way that Professor Bayés de Luna does it: mixing evidence-based medicine with his profuse clinical experience. One can find "tips" and "pearls of wisdom" in almost every page.

I invite you to enjoy this "book of the author", where you will be able to navigate through the lessons of one of the *ECG Masters of the World*. I am sure that you will enjoy it as much as I did in collaborating to produce this amazing second edition.

I would like to dedicate this book to all those in the world who, despite personal difficulties and limitations, wake up every day with the certainty that a better world is possible. My recognition to my mentors and students, the force behind every project I face. My love and gratitude to my wife and daughter, Barbara and Gala, for the joy of life.

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Adrian Baranchuk
Queen's University, Kingston, Ontario, Canada
June 2017

Recommended General Bibliography

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Part I

Anatomical and Electrophysiological Considerations, Clinical Aspects, and Mechanisms of Cardiac Arrhythmias

1

Clinical Aspects of Arrhythmias

Definition of Arrhythmia

Arrhythmias are defined as **any cardiac rhythm other than the normal sinus rhythm.** Sinus rhythm originates in the sinus node. The electrocardiographic characteristics of normal sinus rhythm are:

- An impulse originated in sinus node initiates a positive P wave in I, II, VF, V_2-V_6, and positive or ± in leads III and V_1 that is transmitted through the atria, the atrioventricular (AV) junction, and the intraventricular specific conduction system (ISCS).
- In the absence of pre-excitation, the PR interval ranges from 0.12 to 0.20 s.
- At rest, the sinus node discharge cadence tends to be regular, although it presents generally slight variations, which are usually not evident by palpation or auscultation. However, under normal conditions, and particularly in children, it may present slight to moderate changes dependent on the phases of respiration, with the heart rate increasing with inspiration.
- In adults at rest, the rate of the normal sinus rhythm ranges from 60 to 80 beats per minute (bpm). Thus, sinus rhythms over 80 bpm (sinus tachycardia) and those under 60 bpm (sinus bradycardia) may be considered arrhythmias. However, it should be taken into account that sinus rhythm varies throughout a 24-h period, and sinus tachycardia and sinus bradycardia usually are a physiologic response to certain sympathetic (exercise, stress) or vagal (rest, sleep) stimuli. Under such circumstances, the presence of these heart rates is normal.
- As already stated, it is normal to observe a certain variation of the heart rate during 24 hours. Thus, the evidence of a completely fixed heart rate both during the day and at night is suggestive of arrhythmia. In addition, it is important to remember that:
  (i) **The term arrhythmia does not mean rhythm irregularity**, as regular arrhythmias can occur, often with absolute stability (flutter, paroxysmal tachycardia, etc.), sometimes presenting heart rates in the normal range, as is the case with the flutter 4×1. On the other hand, some irregular rhythms should not be considered arrhythmias (mild to moderate irregularity in the sinus discharge, particularly when linked to respiration, as already stated).
  (ii) **A diagnosis of arrhythmia in itself does not mean evident pathology**. In fact, in healthy subjects, the sporadic presence of certain arrhythmias, both active (premature complexes) and passive (escape complexes, certain degree of AV block, evident sinus arrhythmia, etc.) is frequently observed.

Classification

There are different ways to classify cardiac arrhythmias:

- **According to the site of origin**: arrhythmias are divided into supraventricular (including those having their origin in the sinus node, the atria, and the AV junction), and ventricular arrhythmias.
- **According to the underlying mechanism**: arrhythmias may be explained by (i) abnormal formation of impulses, which includes increased heart automaticity (extrasystolic or parasystolic mechanism) and triggered electrical activity, (ii) reentry of different types, and (iii) decreased automaticity and/or disturbances of conduction (see Chapter 3).
- **From the clinical point of view** arrhythmias may be **paroxysmal, incessant, or permanent**. In reference to tachyarrhythmias (an example of an active arrhythmia, see later), paroxysmal tachyarrhythmias occur suddenly and usually disappear spontaneously (i.e., AV junctional reentrant paroxysmal tachycardia); permanent tachyarrhythmias are always present (i.e., permanent atrial fibrillation); and incessant tachyarrhythmias are characterized by short and repetitive runs of supraventricular (Figure 4.21) or ventricular (Figure 5.4) tachycardia. Extrasystoles may also occur in a paroxysmal or incessant way (see Chapter 3, Mechanisms Responsible for Active Cardiac Arrhythmias). Some bradyarrhythmias,

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such as advanced AV block (an example of passive arrhythmia, see later), may also occur in a paroxysmal or permanent form.

- **From an electrocardiographic point of view**, arrhythmias may be divided into two different types: active and passive (Table 1.1):
  - **Active arrhythmias** due to increased automaticity, reentry, or triggered electrical activity (see Chapter 3 and Table 3.1) generate isolated or repetitive premature complexes on the electrocardiogram (ECG), which occur before the cadence of the regular sinus rhythm. The isolated premature complexes may be originated in a parasystolic or extrasystolic ectopic focus. The extrasystolic mechanism presents a fixed coupling interval, whereas the parasystolic presents a varied coupling interval. Premature complexes of supraventricular origin (p′) are generally followed by a narrow QRS complex, although they may be wide if are conducted with aberrancy. The ectopic P wave (P′) is often not easily seen as it may be hidden in the preceding T wave. In other cases the premature atrial impulse remains blocked in the AV junction, initiating a pause instead of a premature QRS complex (Figures 4.1C and 7.3). The premature complexes of ventricular origin are not preceded by an ectopic P wave, and the QRS complex is always wide (≥0.12 s), unless they originate in the upper part of the intraventricular specific conduction system (see Chapter 5, Electrocardiographic Diagnosis).

    Premature and repetitive complexes include all types of supraventricular or ventricular tachyarrhythmias (tachycardias, fibrillation, flutter). In active cardiac arrhythmias due to reentrant mechanisms, a unidirectional block exists in some part of the circuit (Figure 3.6).
  - **Passive arrhythmias** occur when cardiac stimuli formation and/or conduction are below the range of normality due to a depression of the automatism and/or a stimulus conduction block in the atria, the AV junction, or the specific intraventricular conduction systems (ICS).

    From an electrocardiographic point of view, many passive cardiac arrhythmias present isolated late complexes (**escape complexes**) and, if repetitive, slower than expected heart rate (bradyarrhythmia). Even in the absence of bradyarrhythmia, some type of conduction delay or block in some portion of the specific conduction system (SCS) may exist, for example, first-degree or some second-degree sinoatrial or AV blocks, or atrial or ventricular (bundle branch) blocks. The latter encompasses the aberrant conduction phenomenon (see Chapter 3, Aberrant Conduction). Thus, the electrocardiographic diagnosis of passive cardiac arrhythmia can be made because it may be demonstrated that the ECG changes are due to a depression of automatism and/or conduction in some part of the SCS, without this manifesting in the ECG as a premature complex, as it does in reentry (Figure 3.6).
- Atrial or ventricular blocks are not usually considered arrhythmias. But in our opinion, they should be included as passive cardiac arrhythmias like other types of blocks (sinoatrial or AV). This is why they have been included in this book (see Chapter 3, Heart Block, and Chapter 6, Atrial Blocks, and Ventricular Blocks).

Table 1.1 Classification of arrhythmias according to their electrocardiographic presentation.

Active arrhythmias	Passive arrhythmias
Supraventricular	Escape complex
• Premature complexes	Escape rhythm
• Tachyarrhytmias	Sinus bradycardia
– Different types of tachycardia	Sinoatrial block
– Atrial fibrillation	Atrial block
– Atrial flutter	Atrioventricular block
• Ventricular	Ventricular block
• Premature complexes	Aberrant conduction
• Different types of tachycardia	Cardiac arrest
• Ventricular flutter	
• Ventricular fibrillation	

Clinical Significance and Symptoms

The incidence of the majority of arrhythmias increases progressively with age and arrhythmias are not frequent in children. Data from the Holter ECG recordings (see Appendix A-3, Holter electrocardiographic monitoring and related techniques) have demonstrated that isolated premature ventricular complexes (PVC) are present in about 10–20% of young people in 24-h recordings, and their presence is nearly a rule in the 80+ age group. Similarly, sustained chronic arrhythmias, such as atrial fibrillation, are exceptional in children and are present in about 10% of subjects over 80 years of age. However, **there are arrhythmias that arise particularly in children**, such as some paroxysmal and incessant AV junctional reentrant tachycardias (AVJRT), as well as some monomorphic ventricular tachycardias (idiopathic) and polymorphic ventricular tachycardias (catecholaminergic).

In this book devoted to providing the basis for the diagnosis, prognosis, and treatment of arrhythmias, **active and passive classification of arrhythmias** is used (Table 1.1):

- Active cardiac arrhythmias include isolated or repetitive impulses that command heart rhythm, instead of the basic normal sinus rhythm. They are recorded on the ECG tracing as isolated (premature supraventricular or ventricular complexes), repetitive (named runs), or sustained complexes (different types of tachyarrhythmias).
- Many passive cardiac arrhythmias show isolated or repetitive sinus or escape complexes in the ECG tracings with an abnormally slowed heart rate (bradyarrhythmias). This may be due to depression of automaticity or sinoatrial or AV block. However, in some cases the mechanism responsible for the passive cardiac arrhythmia is delayed conduction, which may modify the ECG pattern (first-degree AV block, or atrial or ventricular bundle branch block), but this does not mean that the heart rate has to be slow.

The most important clinical significance of arrhythmias is related to an association with sudden cardiac death (Goldstein *et al*., 1994; Recommended General Bibliography p. xvii). It is also important to remember that frequently arrhythmias (especially atrial fibrillation) may lead to embolism, including cerebral emboli, often with severe consequences. Also, it must be remembered that sometimes fast arrhythmias may trigger or worsen heart failure (HF). These aspects will be commented on.

Arrhythmias and Sudden Death (SD)

Some of the most important aspects of SD, a true epidemic of the twenty-first century, will now be examined here. In other parts of the book (Chapters 8–11) specific aspects of SD in relation to different heart diseases or situations are discussed in more detail.

Epidemiology

Sudden death is probably the most challenging issue in modern cardiology, taking into account the remarkably high number of SD cases (the estimated number of SD in the United States is approximately 400 000 cases per year, although in Mediterranean countries, such as Spain, the incidence is lower) (Keys and Keys, 1975; Masiá *et al*., 1998; Marrugat *et al*., 1999; Sans *et al*., 2005) and the important social impact of SD events.

Even though SD has been reported in newborns, in whom it has been related to repolarization disorders, alterations of the autonomic nervous system (ANS), and an increase of vagal tone (see Chapter 11, Sudden Infant Death Syndrome), it is indeed very rare in the first decades of life. At this age it often occurs during sports activities (Bayés de Luna *et al*., 2000) and is often associated with inherited heart disease (hypertrophic cardiomyopathy, arrhythmogenic right ventricular dysplasia/cardiomyopathy, and channelopathies). The incidence of SD gradually but significantly increases after 35–40 years of age and is particularly high during the acute phase of myocardial infarction (MI). It is also frequent during the chronic phase of ischemic heart disease (IHD), as well as in subjects with any heart disease, especially when heart failure (HF) is present (Myerburg *et al*., 1997) (Figure 1.1).

Associated Diseases

As previously discussed, acute IHD is frequently associated with SD in adults. In the majority of cases of SD outside acute IHD or channelopathies, HF, or at least left ventricular dysfunction, is present. HF may be idiopathic or present in patients with chronic IHD, hypertension, cardiomyopathies, and so on. More details on this association are shown in Chapter 11 (see Chapter 11, Ischemic

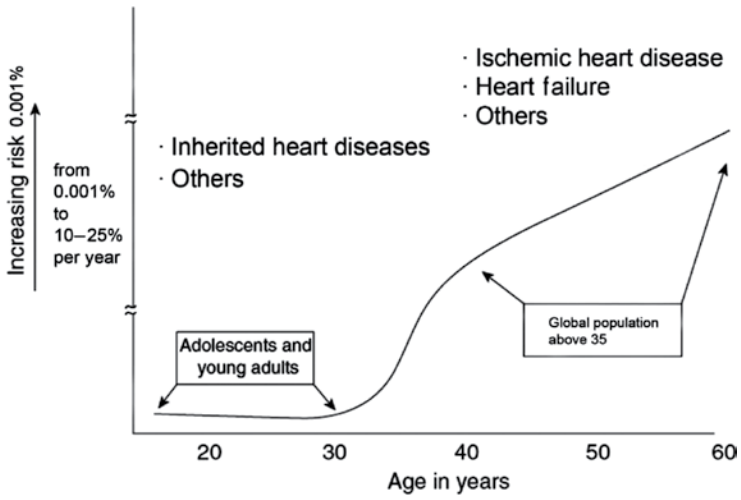

Figure 1.1 Relationship between the incidence of sudden death (SD) and age. Note that the sudden death may also be associated with different diseases along the life period (Myerburg *et al*., 1992).

Heart Disease, and Heart Failure). Inherited heart disease (InHD) can cause SD at any age but the overall impact is small (Figure 1.1). It should be emphasized, however, that it is responsible for the majority of cases of SD that occur before the age of 35 years. InHD appears more in men and may occur during exercise (cardiomyopathies) or sleep or rest (channelopathies) (see Chapter 9).

We performed a study (the EULALIA trial) that included 204 cases of SD occurring in the Mediterranean area (Subirana *et al.*, 2011). In this study, the epidemiological and pathological aspects of diseases associated with SD were analyzed. Table 1.2 shows the diagnosis obtained by the pathologists. When compared with other similar Anglo-Saxon studies (Burke *et al.*, 1997), what caught our attention was that the number of cases presenting with IHD found at autopsy, as well as the incidence of acute thrombosis, as an anatomopathologic expression of MI, was lower than in previously published Anglo-Saxon studies (80–90% vs 58% and 52% vs 40% for IHD and acute thrombosis, respectively) (Figure 1.2). Our findings are concordant with previously known evidence (Keys and Keys 1975; de Lorgeril *et al.*, 1999; Marrugat *et al.*, 1999; Sans *et al.*, 2005) that the incidence of IHD in Mediterranean regions is lower, probably related to diet, lifestyle, and environment (Mediterranean culture). In contrast, SD victims from the Mediterranean region presented left ventricular hypertrophy more frequently than other studies (48% vs 20%) (Virmani *et al.*, 2001; Subirana *et al.*, 2011). From a clinical point of view, the victims of SD in the EULALIA trial presented anginal episodes less frequently (20% vs 37%), which was in agreement with the reduced number of cases with IHD found at autopsy, when compared with the Maastricht study (de Vreede-Swagemakers *et al.*, 1997). In our series, the incidence of associated InHD was 3% (hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy). In approximately 7% of cases autopsy did not reveal any changes. Some of these cases might be explained by channelopathies (Table 1.2).

Table 1.2 Sudden death victims: pathological abnormalities found in necropsy.

Sudden death victims (n = 204)	N	%
Cardiovascular diseases (n = 183)		
Heart diseases (n = 161)		
Ischemic heart disease	119	58.4
Hypertensive heart disease	20	9.9
Valvular diseases	5	2.4
Idiopathic left ventricular hypertrophy	4	1.9
Dilated cardiomyopathy	4	1.9
Hypertrophic cardiomyopathy	3	1.5
Arrhythmogenic RV dysplasia/ cardiomyopathy	3	1.5
Myocarditis	1	0.5
Congenital heart disease	1	0.5
Amyloidosis	1	0.5
Vascular diseases (n = 22)		
Pulmonary embolism	8	3.9
Dissection of the aorta	9	4.4
Cerebral hemorrhage	5	2.4
Nonvascular diseases (n = 7)		
Gastrointestinal disorders	3	1.5
Pulmonary disorders	4	1.9
Without findings	14	6.9

Taken from Subirana *et al.*, 2011.

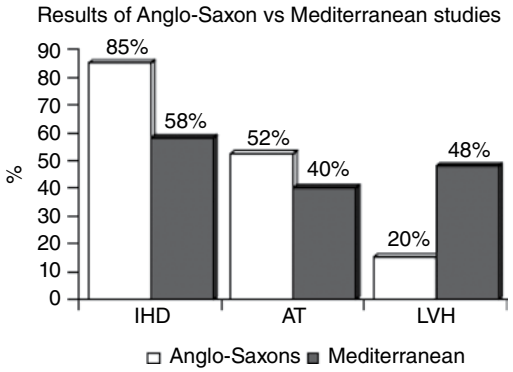

Figure 1.2 Comparative study on the incidence of ischemic heart disease (IHD), acute thrombosis (AT), and left ventricular hypertrophy (LVH) in the EULALIA trial.

The majority of SD cases occur in subjects with ischemic heart disease and/or heart failure. It must be emphasized that heart failure is most frequently related to hypertension, chronic ischemic heart disease, cardiomyopathies, and valvular heart disease.

Inherited heart diseases are the main cause of SD in the first decades of life.

Chain of Events Leading to Final Arrhythmias and SD

SD is the final stage of a chain of events that ends in cardiac arrest, usually due to ventricular fibrillation (VF) or, less frequently, extreme bradyarrhythmia (Bayés-Genis *et al.*, 1995). In all cases there are a number of modulating and/or triggering factors that act on the vulnerable myocardium precipitating SD. Figure 1.3 shows this chain of events in different heart diseases. Ventricular fibrillation (VF) can appear without previous VT, triggered by a PVC in the presence of other modulating or triggering factors (including genetic and environmental),

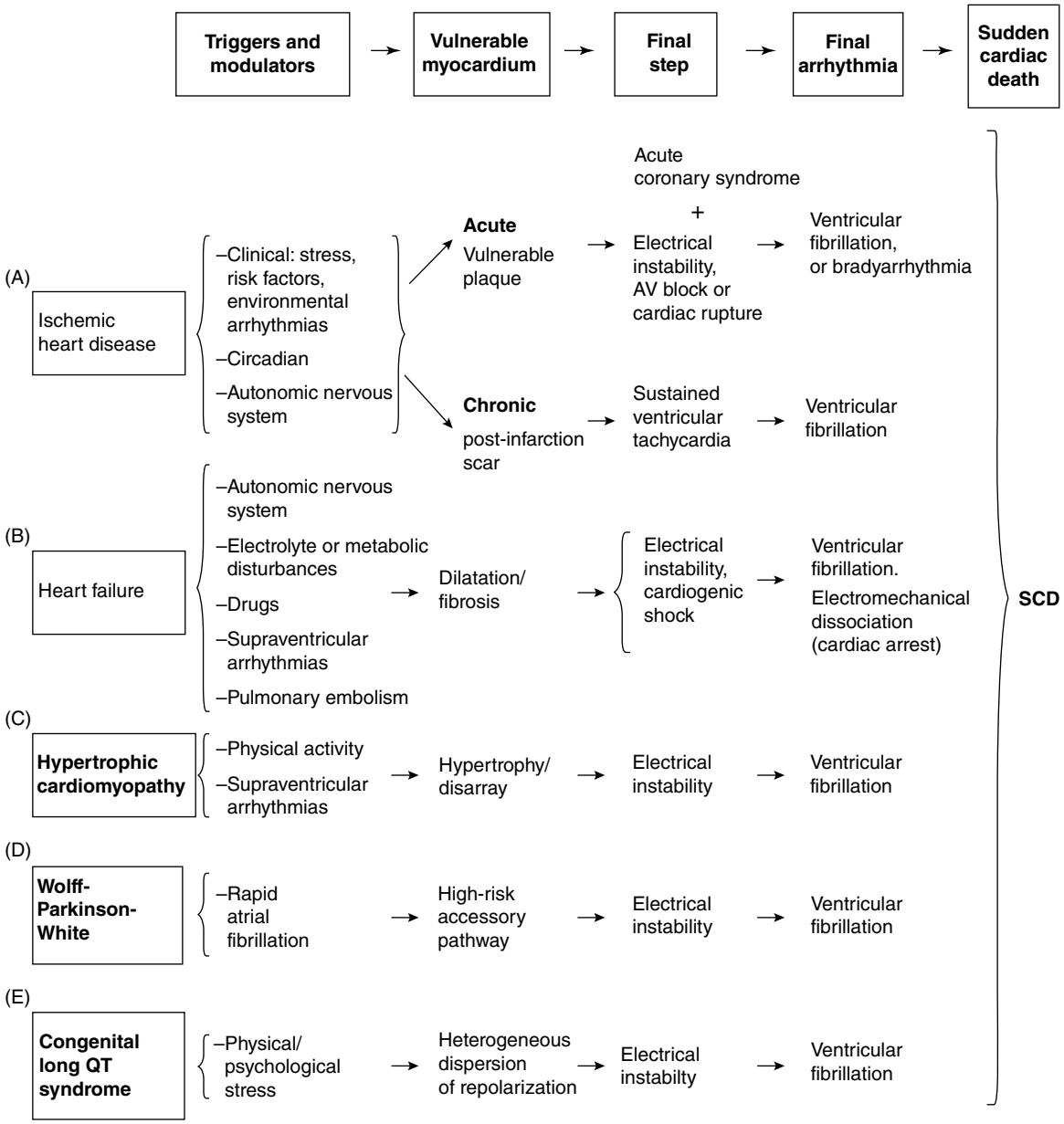

Figure 1.3 Chain of events that trigger cardiac sudden death (CSD) and parameters that different diseases present at the different stages leading to CSD (adapted from Bayés-Genis *et al*., 1995).

and/or the sympathetic overdrive secondary to physical or mental stress. Usually under normal circumstances, probably all of these factors would not be of any consequence, but in the presence of acute ischemia they may trigger SD (Figure 1.5). The VF may be secondary to classic monomorphic sustained VT (Figure 1.4) or Torsades de Pointes VT (Figure 1.6). Sudden death is seldom a consequence of bradyarrhythmia (Figure 1.7).

Therefore, the final arrhythmias that precipitate SD are not always the same (Figures 1.4–1.8). In a study that we performed revising the final causes of SD in 157 ambulatory patients who died suddenly while wearing a Holter recorder (Bayés de Luna *et al*., 1989), it was found that in two-thirds of patients SD was caused by **sustained VT that precipitated** VF (Figure 1.8, Table 1.3). This was generally accompanied by fast baseline heart rate (sinus tachycardia or rapid atrial fibrillation), which may be considered a sign of sympathetic overdrive (Figure 1.4). VF without previous VT, usually associated with acute IHD, is more frequently seen as a consequence of PVCs with an R/T phenomenon. In our experience with ambulatory patients this pattern was observed in less than 10% of cases (Figure 1.5). Curiously, in 13% of cases, SD was due to Torsades de Pointes VT precipitating VF, generally

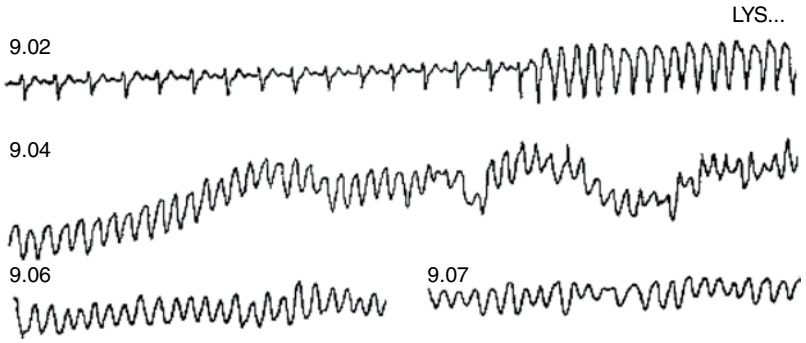

Figure 1.4 Ambulatory sudden death due to a ventricular fibrillation (VF) in an ischemic heart disease patient treated with amiodarone for frequent premature ventricular complexes. At 9:02 a.m. he presented a monomorphic sustained ventricular tachycardia (VT), followed by a VF at 9:04 a.m. after an increase in VT rate and width of QRS complex.

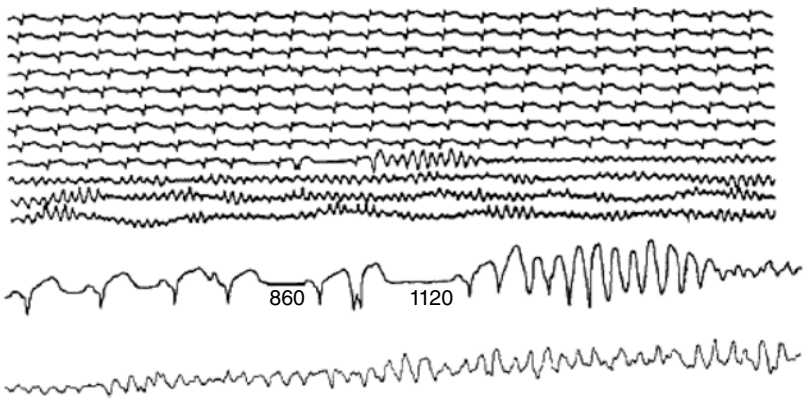

Figure 1.5 Ambulatory sudden death due to a primary ventricular fibrillation (VF) triggered by a premature ventricular complex (PVC) with a short coupling interval, after a post-PVC pause (1120 ms) longer than the previous one (860 ms). Note that the sequence of events started with an atrial premature complex, which caused the first shorter pause.

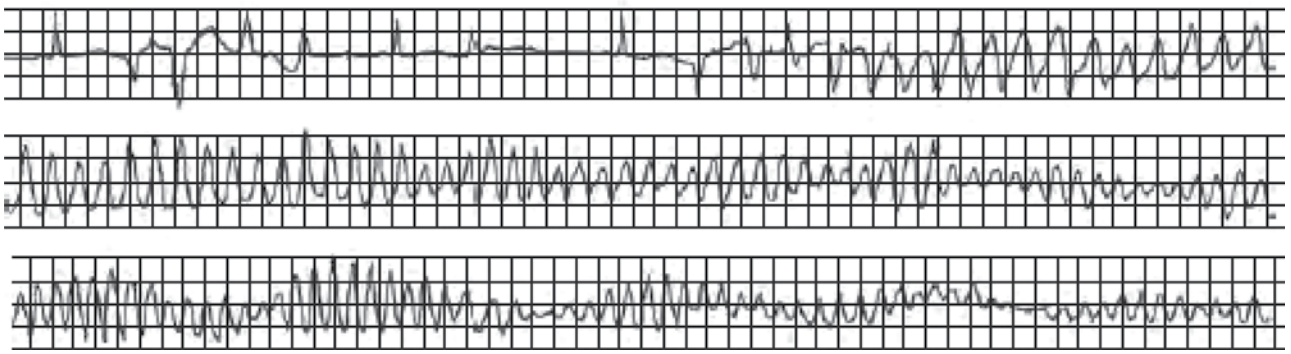

Figure 1.6 Beginning of a Torsades de Pointes ventricular tachycardia (VT) in a woman without ischemic heart disease treated with quinidine for runs of nonsustained VT. The Torsades de Pointes VT triggered a ventricular fibrillation (VF).

in patients without severe heart disease but taking antiarrhythmic Class I type drugs because of nonfrequent ventricular arrhythmias, sometimes isolated PVCs (proarrhythmic effect). We believe that if this study were performed now, the number of cases would be much smaller due to the evidence shown by the CAST study (Echt *et al*., 1991) demonstrating that class I antiarrhythmic agents are dangerous, especially in patients with heart disease. Thus, currently the prescription of class I antiarrhythmic drugs in post-MI patients is much lower. Finally, cases of SD due to extreme bradyarrhythmia (≈15% in our study) (Figure 1.8B) were related more to progressive depression of the sinus node and AV node automatism (Figure 1.7) than to AV block.

Figure 1.8 shows the final arrhythmias that cause SD in patients with different clinical settings: (A) in a mobile coronary care unit on route to hospital due to an acute coronary syndrome (Adgey *et al*., 1982), (B) in ambulatory patients (Holter recording) (Bayés de Luna *et al*., 1989), and (C) in patients hospitalized because of severe HF (Luu *et al*., 1989). In the first situation (A), there are more cases of without previous VT than in our ambulatory cohort (B), most probably because patients in group A were in the acute phase of a MI. On the other hand,

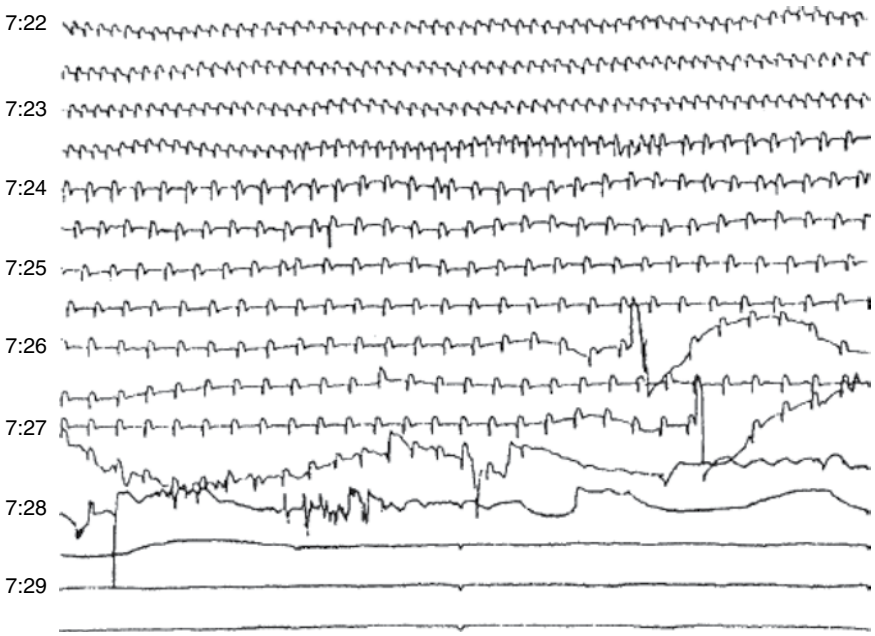

Figure 1.7 Sudden death due to a progressive bradycardia in a patient with acute infarction and electromechanical dissociation.

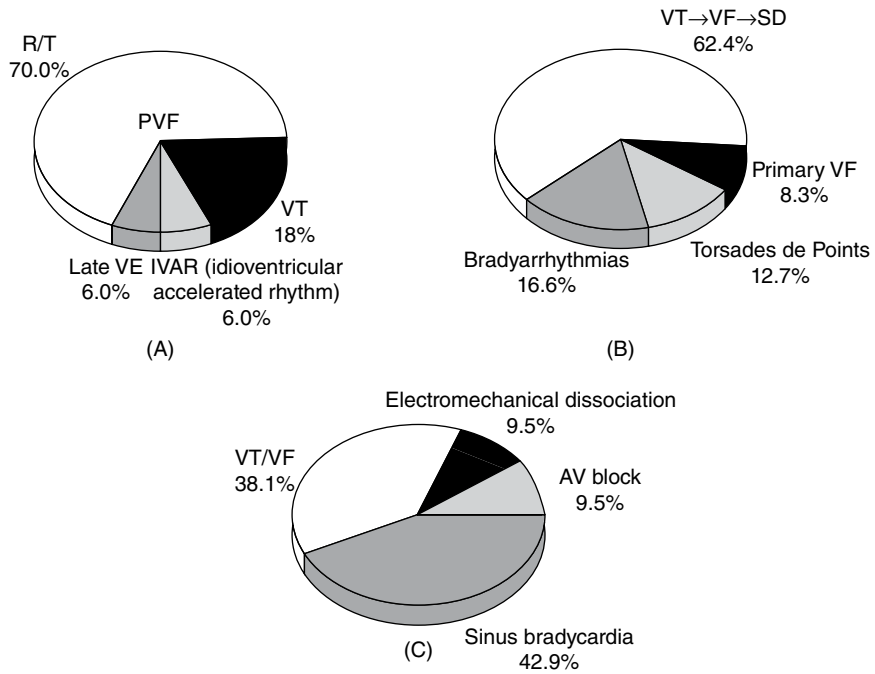

Figure 1.8 Sudden death: final arrhythmias. (A): in patients with acute ischemic heart disease (Adgey *et al*., 1982). (B): in ambulatory patients wearing a Holter monitor, in whom a depressed ejection fraction was present in 80% of cases (Bayés de Luna *et al*., 1989). (C): in patients with advanced heart failure (Luu *et al*., 1989).

patients with severe HF (group C) presented extreme bradyarrhythmias more frequently as a cause of SD. This could be the reason why antiarrhythmic drugs are not efficient in preventing SD in patients with severe HF. In our series (Figure 1.8B), 80% of patients had a depressed ejection fraction (EF), although their functional class was acceptable. These patients were "too healthy to die", and many of these cases of SD could have been prevented with adequate therapy that sometimes consists of not prescribing an antiarrhythmic agent. The Hippocratic Oath must be remembered: "c", "First, do no harm".

Our results were similar to those demonstrated in patients treated with implantable cardioverter defibrillators (ICD) with or without cardiac resynchronization therapy (CRT) (ICD-CR). In these cases, fast VTs also frequently appeared and were treated by antitachycardia pacing (Leitch *et al*., 1991; Grimm *et al*., 2006). In contrast, in a small series of post-MI patients with an EF <40%, using an insertable loop recorder, who died