

Stress Echocardiography

Eugenio Picano

Stress Echocardiography

**Fifth, Completely Revised
and Updated Edition**



Springer

Eugenio Picano MD, PhD

Director General

Institute of Clinical Physiology of Pisa

National Research Council

1st Fisiologia Clinica

Via G. Moruzzi, 1

56124 Pisa

Italy

ISBN: 978-3-540-76465-6

e-ISBN: 978-3-540-76466-3

DOI: 10.1007/978-3-540-76466-3

Library of Congress Control Number: 2008940140

© 2009 Springer-Verlag Berlin Heidelberg

This work is subject to copyright. All rights are reserved, whether the whole or part of the material is concerned, specifically the rights of translation, reprinting, reuse of illustrations, recitation, broadcasting, reproduction on microfilm or in any other way, and storage in data banks. Duplication of this publication or parts thereof is permitted only under the provisions of the German Copyright Law of September 9, 1965, in its current version, and permission for use must always be obtained from Springer. Violations are liable to prosecution under the German Copyright Law.

The use of general descriptive names, registered names, trademarks, etc. in this publication does not imply, even in the absence of a specific statement, that such names are exempt from the relevant protective laws and regulations and therefore free for general use.

Product liability: The publishers cannot guarantee the accuracy of any information about dosage and application contained in this book. In every individual case the user must check such information by consulting the relevant literature.

Cover design: Frido Steinen-Broo, eStudio Calamar, Spain

Printed on acid-free paper

9 8 7 6 5 4 3 2 1

springer.com

Preface

This book has a past. Its various editions parallel the growth of stress echocardiography within the scientific community and the clinical arena. The first edition in 1991 consisted of 100 pages, which increased to 200 in the second (1994), 300 in the third (1997), nearly 500 pages in the fourth, and finally more than 600 in the current fifth edition. The general perception of stress echocardiography has changed in the cardiology community. No longer a promising innovation viewed with a mixture of suspicion and attraction, it is now an established technique with the huge potential to resolve the present paradox of saving health care money while at the same time improving diagnostic standards. In a cardiological climate where inappropriate, redundant, and often risky imaging examinations proliferate, stress echocardiography offers the great advantage of being relatively low cost, free of biohazards for the patient, and causing no ecological stress on the planet. By choice and by necessity, modern, responsible diagnosis with cardiac imaging must be economical, ecological, and therefore usually echocardiographic. Another major change has taken place in stress echocardiography laboratories during the last 5 years, making a new edition of the book mandatory. For a long time, the scope and application of stress echocardiography remained focused on coronary artery disease. In the last few years, it has exploded in its breadth and variety of applications, enjoying the tremendous technological and conceptual versatility that this technique offers. Nowadays, in the stress echocardiography laboratory we assess not only left ventricular function, but also coronary artery flow, valve gradients, intraventricular pressures, and pulmonary hemodynamics. We stress not only coronary arteries, but also the valves, myocardium, vessels, alveolar–capillary barrier in the lung, and peripheral and pulmonary circulation. Ten years ago, only patients with known or suspected coronary artery disease entered the stress echocardiography laboratory, and only regional wall motion was assessed. Now, we evaluate coronary artery disease as well as cardiomyopathy, valvular heart disease, children with congenital heart disease, and patients with incipient or advanced vascular disease. For each patient, we can tailor a dedicated stress with a specific method to address a particular diagnostic question. Thirty years ago, Harvey Feigenbaum – one of the founding fathers of modern echocardiography – stated that it is not possible to understand the cardiac patient without the help of resting transthoracic echocardiography. After 30 years, we can safely state that it is not possible to understand the cardiac patient without the help of stress echocardiography. The book was single authored in the first edition, and then enjoyed many distinguished contributors in its subsequent editions, up to the record number of 29 contributors in the present edition. They come from 15 countries spanning four continents and represent, in

my opinion, some of the best available knowledge and expertise in their respective fields. I am proud and honored that they accepted the invitation to be a part of this project. At the same time, I aimed to avoid the fragmentation, gaps, and inconsistencies of a multiauthor text; therefore, I painfully decided to draft the first version of each chapter – then asked for corrections, revisions, cuts, additions, and integrations from more knowledgeable contributors. To all of them and to the junior and senior colleagues who have worked with me over the last 30 years – far too many to be mentioned here – *grazie*.

Pisa, February 2009

Eugenio Picano

Contents

Section 1 Basic Principles, Methodology and Pathophysiology

1 Stress Echocardiography: A Historical and Societal Perspective	3
Eugenio Picano	
1.1 Dawn of the Stress Echocardiography Era: From Experimental Studies to the Monodimensional Approach	3
1.2 Second-Generation Stress Echocardiography: Pharmacological Stresses in the 2D Era	5
1.3 Third-Generation Stress Echocardiography Today: Coronary Flow Reserve and Dual Imaging	7
1.4 Cardiac Imaging and Its Guidelines.....	9
1.5 Cardiac Imaging and the Radiation-Induced Biorisks.....	11
1.6 Cardiac Imaging and the Regulatory Framework	14
1.7 Cardiac Imaging in the Age of Sustainability: The “Eco-Eco-Echo” Diagnosis	15
References.....	16
2 Anatomical and Functional Targets of Stress Testing	19
Eugenio Picano	
2.1 Pathways of Ischemia.....	19
2.2 Epicardial Coronary Arteries	19
2.3 Fixed Stenosis	20
2.4 Dynamic Stenosis	21
2.5 Myocardium and Small Coronary Vessels	21
2.6 The Target of Ischemia: The Subendocardial Layer.....	23
2.7 The Diagnostic “Gold Standard”: Pure Gold?	23
References.....	28
3 Symptoms and Signs of Myocardial Ischemia.....	31
Eugenio Picano	
3.1 Chest Pain	31
3.2 Electrocardiographic Changes	33

3.3	Alterations in Left Ventricular Function	33
3.4	Perfusion Abnormalities.....	34
3.5	The Paradigm Challenged: The Alternative Ischemic Cascade	35
3.6	Equations in the Diagnosis of Ischemia.....	38
3.7	A New Diagnostic Variable: Coronary Flow Reserve.....	39
	References.....	40
4	Rational Basis of Stress Echocardiography	43
	Fabio Recchia and Eugenio Picano	
4.1	Biochemical Basis.....	43
4.2	Physiological Heterogeneity of Myocardial Function	44
4.3	Regional Flow–Function Relationship in Myocardial Ischemia.....	48
4.4	Postischemic Recovery of Contractile Function	49
4.5	Determinants of Regional Dysfunction	51
4.6	Clinical Basis	53
	References	53
5	Pathogenetic Mechanisms of Stress	57
	Eugenio Picano	
5.1	Ischemia and Vasospasm.....	57
5.2	Increased Demand.....	60
5.3	Flow Maldistribution.....	62
5.4	Exercise-Simulating Agents: Scientific Fact or Fancy Definition?	65
5.5	New Pharmacological Stresses	67
5.6	The Atropine Factor in Pharmacological Stress Echocardiography.....	67
5.7	The Combined Stress Approach	67
5.8	Vasodilatory Power and the Hierarchy of Testing	69
5.9	The Fosbury Flop and the Classic Straddle in the Stress Echocardiography Laboratory	70
	References	71
6	Echocardiographic Signs of Ischemia	75
	Eugenio Picano	
6.1	The Main Sign of Ischemia with 2D Echocardiography:	75
6.1.1	Regional Asynergy.....	75
6.2	Stress Echocardiography in Four Equations	79
6.2.1	False-Negative Results	80
6.3	False-Positive Responses	81
6.3.1	“False” Stress Echocardiography Results: Anatomic Lies and Prognostic Truths?	83
	References.....	86

7 Segmentation of the Left Ventricle	91
Eugenio Picano	
7.1 The 17-Segment Model.....	93
7.2 Assignment of Segments to Coronary Arterial Territories.....	94
7.3 Left Ventricular Function in a Number	96
7.4 Artifactual Pseudoasynnergies.....	99
7.5 Matching Between TTE and TEE Segments.....	99
7.6 Left Ventricular Segments: Matching Between 2D and 3D Imaging.....	101
References.....	102
 8 Dynamic and Pharmacologic Right Heart Stress Echocardiography: Right Ventricular Function, Right Coronary Artery Flow, Pulmonary Pressure, and Alveolar–Capillary Membrane Testing in the Echocardiography Laboratory	 105
Eugenio Picano, Ekkehard Grünig, Alberto San Román, Kwan Damon, and Nelson B. Schiller	
8.1 Regional Right Ventricular Function in Coronary Artery Disease	106
8.2 Measurement of Global Right Ventricular Function by Planimetry and Descent of the Right Ventricular Base.....	108
8.3 Coronary Flow Reserve of the Right Coronary Artery.....	110
8.4 Pulmonary Hemodynamics.....	112
8.5 Ultrasound Lung Comets	116
8.6 Conclusion	118
References.....	119
 9 Coronary Flow Reserve	125
Fausto Rigo, Jorge Lowenstein, and Eugenio Picano	
9.1 Historical Background and Physiological Basis	125
9.2 Coronary Flow Reserve in the Echocardiography Laboratory	128
9.3 Methodology of Coronary Flow Reserve Testing	131
9.4 Coronary Flow Reserve: The Diagnostic Results	135
9.5 The Prognostic Value of Coronary Flow Reserve.....	137
9.6 Targets, Tips, and Traps in Coronary Flow Reserve	138
9.7 Coronary Flow Reserve in the Stress Echocardiography Laboratory: Here to Stay.....	139
References.....	141

10 Technology and Training Requirements.....	145
Eugenio Picano	
10.1 General Test Protocol.....	145
10.2 Imaging Equipment and Techniques.....	147
10.3 Training Requirements.....	148
10.4 The Most Frequent Mistakes.....	152
References.....	154
 Section 2 Stresses: How, When and Why	
11 Exercise Echocardiography.....	159
Luc A. Piérard and Eugenio Picano	
11.1 Historical Background.....	159
11.2 Pathophysiology.....	160
11.3 Exercise Techniques.....	163
11.4 Safety and Feasibility.....	165
11.5 Diagnostic Results for Detection of Coronary Artery Disease and Myocardial Viability.....	166
11.6 Prognostic Value.....	167
11.7 Indications and Contraindications to Exercise Stress Echocardiography.....	169
References.....	170
 12 Dobutamine Stress Echocardiography.....	175
Eugenio Picano	
12.1 Historical Background.....	175
12.2 Pharmacology and Pathophysiology.....	175
12.3 Methodology.....	176
12.4 Feasibility and Safety.....	178
12.5 Diagnostic Results for Detection of Coronary Artery Disease.....	179
12.6 Identification of Myocardial Viability.....	180
12.7 Prognostic Value.....	181
12.8 Indications and Contraindications.....	182
References.....	183
 13 Dipyridamole Stress Echocardiography.....	189
Eugenio Picano	
13.1 Historical Background.....	189
13.2 Pharmacology and Pathophysiology.....	192
13.3 Methodology.....	193

13.4	Feasibility and Safety	194
13.5	Diagnostic Results for Detection of Coronary Artery Disease	194
13.6	Viability	196
13.7	Prognostic Value.....	197
13.8	Indications and Contraindications.....	199
	References.....	201
14	Adenosine Stress Echocardiography.....	207
	Eugenio Picano, Miodrag Ostojic, and Rodolfo Citro	
14.1	Historical Background.....	207
14.2	Pharmacology and Pathophysiology.....	208
14.3	Methodology	212
14.4	Tolerability and Safety.....	212
14.5	Diagnostic Accuracy for Detection of Coronary Artery Disease and Myocardial Viability	213
14.6	Prognostic Value.....	215
14.7	Indications and Contraindications.....	215
	References.....	216
15	Pacing Stress Echocardiography.....	221
	Eugenio Picano	
15.1	Historical Background.....	221
15.2	Pathophysiology.....	221
15.3	Methodology	223
15.4	Clinical Results and Comparison with Other Stress Echocardiography Tests	225
15.5	Limitations and Indications.....	225
	References.....	227
16	Ergonovine Stress Echocardiography for the Diagnosis of Vasospastic Angina	229
	Jae-Kwan Song and Eugenio Picano	
16.1	Basic Considerations.....	229
16.2	Protocol.....	230
16.3	Noninvasive Diagnosis of Coronary Artery Spasm: Clinical Data	231
16.4	Special Safety Considerations.....	232
16.5	Clinical Impact.....	235
	References.....	237

17 Hyperventilation Test	241
Eugenio Picano	
17.1 Pathophysiology.....	241
17.2 Protocol.....	241
17.3 Diagnostic Value	242
17.4 Diagnostic Value and Clinical Guidelines.....	243
References.....	245
18 Grading of Ischemic Response	247
Eugenio Picano	
18.1 Degree of Asynergy	249
18.2 Extent of Asynergy	249
18.3 Ischemia-Free Stress Time	251
18.4 Slow or Incomplete Recovery	253
18.5 False Friends of Stress-Induced Ischemia Severity: Arrhythmias and Hypotension	253
18.6 The Fourth Coordinate: Perfusion and/or Coronary Flow Reserve	254
18.7 Conclusion	254
References.....	255
19 Diagnostic Results and Indications	259
Eugenio Picano	
19.1 Stress Echocardiography Versus Other Diagnostic Tests	261
19.2 Stress Echocardiography and the Effects of Medical Therapy	265
19.3 Contraindications to Stress Testing	266
19.4 Indications for Stress Testing	268
19.5 Inappropriate Use of Stress Testing	269
References.....	270
20 Myocardial Viability	273
Luc Piérard and Eugenio Picano	
20.1 Historical Background.....	273
20.2 Pathophysiology Behind Viability Imaging	274
20.3 Nuclear and Magnetic Resonance Techniques for the Identification of Myocardial Viability	276
20.4 Resting Echocardiography	278
20.5 Myocardial Contrast Echocardiography	279
20.6 Tissue Characterization and Myocardial Velocity Imaging	280
20.7 Dobutamine Stress Echocardiography	280
20.8 Alternative Stress Echocardiography Methods.....	282
20.9 The Clinical Value of Myocardial Viability: Critical or Luxury Information?	283

20.10	The Prognostic Value of Myocardial Viability: A Moonlight Serenade	286
20.11	Myocardial Viability in Context.....	287
	References.....	289
21	Diagnostic Flowcharts.....	295
	Eugenio Picano	
21.1	Step 1: Clinical Picture	295
21.2	Step 2: Exercise Electrocardiography Stress Test	296
21.3	Step 3: Stress Imaging Testing	298
21.4	Step 4: Testing for Vasospasm.....	300
	References.....	301
22	Prognosis.....	303
	Eugenio Picano	
22.1	Left Ventricular Function	303
22.2	Myocardial Viability	304
22.3	Inducible Ischemia	306
22.4	Pathophysiological Heterogeneity of Different Events.....	308
22.5	Practical Implications.....	309
22.5.1	Comparison of Invasive and Noninvasive Approaches	312
	References.....	313
Section 3 New Technologies and New Diagnostic Targets		
23	New Ultrasound Technologies for Quantitative Assessment of Left Ventricular Function.....	319
	Thomas H. Marwick, Adrian C. Borges, and Eugenio Picano	
23.1	Spatial and Temporal Heterogeneity of Left Ventricular Contraction	320
23.2	<i>M</i> -mode Echocardiography and Longitudinal Function	324
23.3	Anatomical <i>M</i> -mode	325
23.4	Tissue Characterization.....	326
23.5	Color Kinesis	326
23.6	Tissue Doppler Imaging.....	327
23.7	Strain-Rate Imaging	328
23.8	Speckle Tracking.....	331
23.9	Three-Dimensional Echocardiography	331
23.10	Protechnology Bias: A Word of Caution.....	333
23.11	Conclusion – Technology and Teaching.....	337
	References.....	338

24	Contrast Stress Echocardiography	343
	Mark J. Monaghan and Eugenio Picano	
24.1	Historical Background	343
24.2	Pathophysiology of MCE	345
24.3	Physics of Microbubbles and Modalities of Administration	347
24.4	MCE Methodology	349
24.5	Limitation of Stress MCE	353
24.6	Contrast Stress Echocardiography: The Current Indications	355
	References	357
25	Diastolic Stress Echocardiography	361
	Maurizio Galderisi and Eugenio Picano	
25.1	Pathophysiological Basis of Diastolic Dysfunction	362
25.2	The Echocardiography Assessment of Diastolic Function	365
25.3	Clinical Results	366
25.4	A Roadmap to the Future	369
	References	370
26	Endothelial Function in the Stress Echocardiography Laboratory	375
	Eugenio Picano	
26.1	Introduction	375
26.2	Historical Background	376
26.3	Physiology of Normal Endothelium	378
26.4	Methodology of Endothelium-Dependent Flow-Mediated Vasodilation	380
26.5	Diagnostic Value of Endothelial Dysfunction for Detection of Coronary Artery Disease	383
26.6	Prognostic Value of Endothelial Dysfunction	385
26.7	Clinical Implications and Future Perspectives	389
	References	390
Section 4	In Front of The Patient: Clinical Applications in Different Patient Subsets	
27	Special Subsets of Angiographically Defined Patients: Normal Coronary Arteries, Single-Vessel Disease, Left Main Coronary Artery Disease, Patients Undergoing Coronary Revascularization	395
	Eugenio Picano and Rosa Sicari	
27.1	Normal Coronary Arteries	395
27.2	Single-Vessel Disease	396

27.3	Left Main Coronary Artery Disease	397
27.4	Patients Undergoing Coronary Revascularization	398
	References.....	400
28	Special Subsets of Electrocardiographically Defined Patients: Left Bundle Branch Block, Right Bundle Branch Block, Atrial Fibrillation	405
	Eugenio Picano and Lauro Cortigiani	
28.1	Left Bundle Branch Block	405
28.2	Right Bundle Branch Block	406
28.3	Atrial Fibrillation	407
	References.....	410
29	Special Subsets of Clinically Defined Patients: Elderly, Women, Outpatients, Chest Pain Unit, Noncardiac Vascular Surgery	413
	Rosa Sicari, Gigliola Bedetti, and Eugenio Picano	
29.1	Elderly Patients	413
29.2	Women	414
29.3	Outpatients	415
29.4	Chest Pain Unit Patients.....	415
29.5	Noncardiac Vascular Surgery	420
	References.....	422
30	Microvascular Disease	429
	Paolo G. Camici and Eugenio Picano	
30.1	Background	429
30.2	Pathophysiology of Microvascular Angina	432
30.3	Stress Echocardiographic Findings in Cardiac Syndrome X	436
30.4	The Prognostic Heterogeneity of Chest Pain with Angiographically Normal Coronary Arteries	437
30.5	The Diagnostic Flow Chart in Microvascular Angina	443
	References.....	444
31	Hypertension	447
	Eugenio Picano	
31.1	Background	447
31.2	Pathophysiology	447
31.3	Diagnosis of Coronary Artery Disease	449
31.4	Prognostic Stratification	450
	References.....	453

32 Diabetes	457
Eugenio Picano and Lauro Cortigiani	
32.1 Pathophysiology.....	457
32.2 Diagnosis of Coronary Artery Disease	458
32.3 Prognostic Stratification	459
32.4 The Diagnostic Flow Chart in Diabetics.....	460
References.....	462
33 Stress Echocardiography in Dilated Cardiomyopathy	465
Eugenio Picano	
33.1 Incipient or Latent Cardiomyopathy	466
33.2 Dilated Cardiomyopathy	468
33.3 Differentiation Between Ischemic and Nonischemic Dilated Cardiomyopathy	470
33.4 Stress Echocardiography and Cardiac Resynchronization Therapy.....	471
References.....	475
34 Stress Echocardiography in Hypertrophic Cardiomyopathy	479
Eugenio Picano	
34.1 Background.....	479
34.2 Pathophysiology.....	480
34.3 Stress Echocardiographic Findings in HCM.....	482
34.4 Conclusion	484
References.....	485
35 Stress Echocardiography After Cardiac Transplantation	487
Eugenio Picano, Tonino Bombardini, and Giorgio Arpesella	
35.1 Background.....	487
35.2 Pharmacological Stress Echocardiography for Detection of Acute Rejection	488
35.3 Pharmacological Stress Echocardiography for Detection of Chronic Rejection.....	489
35.4 Pharmacological Stress Echocardiography for Recruitment of Donor Hearts.....	493
35.5 Conclusions.....	494
References.....	494

36	The Emerging Role of Exercise Testing and Stress Echocardiography in Valvular Heart Disease.....	499
	Eugenio Picano, Philippe Pibarot, Patrizio Lancellotti, Jean Luc Monin, and Robert O. Bonow	
36.1	Aortic Stenosis.....	501
36.2	Aortic Regurgitation.....	507
36.3	Mitral Stenosis.....	507
36.4	Mitral Regurgitation.....	509
36.5	Prosthetic Heart Valves.....	511
36.6	Coronary Artery Disease and Coronary Flow Reserve.....	514
36.7	Conclusions.....	516
	References.....	516
37	Stress Echocardiography in Children	523
	Eugenio Picano and Michael Henein	
37.1	Pediatric Coronary Artery Disease	523
37.2	Transplant Coronary Artery Disease.....	525
37.3	Transposition of Great Arteries After Surgical Repair.....	526
37.4	Valve and Intraventricular Gradients	528
37.5	Contractile Reserve.....	528
37.6	Coronary Flow Reserve	530
37.7	Conclusions.....	531
	References.....	532
Section 5 Comparison with Other Imaging Techniques		
38	Stress Echocardiography Versus Stress Perfusion Scintigraphy	539
	Thomas H. Marwick and Eugenio Picano	
38.1	Nuclear Cardiology, the Land of Our Fathers	539
38.2	SPECT, PET, and PET–CT Imaging: Advantages and Limitations.....	539
38.3	MPI vs. Stress Echocardiography	540
38.4	Current Clinical Indications.....	542
38.5	The Elephant in the Room – Radiation Safety.....	543
38.6	Conclusion	546
	References.....	548
39	Stress Echocardiography Versus Cardiac CT.....	553
	Eugenio Picano and William Wijns	
39.1	Cardiac Imaging in the CTA Era.....	553
39.2	Advantages and Limitations of Cardiac CTA	555
39.3	Stress Echocardiography vs. Cardiac CTA	556

39.4	Current Clinical Indications.....	559
39.5	Conclusions.....	560
	References.....	563
40	Stress Echocardiography Versus Stress CMR	569
	Eugenio Picano and Juerg Schwitter	
40.1	Coronary Artery Disease Detection by CMR: The Rich Cardiologist's Super Stress Echocardiography?.....	569
40.2	Stress CMR: Advantages and Limitations	570
40.3	Stress Echocardiography vs. Stress CMR.....	572
40.4	Clinical Implications.....	576
	References.....	579
41	Appropriateness in the Stress Echocardiography Laboratory.....	585
	Eugenio Picano	
41.1	The Ulysses Syndrome in the Cardiac Imaging Laboratory.....	586
41.2	Appropriateness in Stress Echocardiography	590
	References.....	594
	Index.....	597

List of Contributors

Giorgio Arpesella

Dipartimento Cardiovascolare
Università di Bologna
Via Massarenti 9
40138 Bologna, Italy

Gigliola Bedetti

Cardiology Division
Imola Hospital
Via Montericco 4
40026 Imola, Italy

Tonino Bombardini

Associate Researcher
Istituto di Fisiologia Clinica
CNR, Via Moruzzi 1
56124 Pisa, Italy

Robert Bonow

Goldberg Professor of Medicine
Division of Cardiology
Northwestern University's Feinberg
School of Medicine
676 St., Claire St., Suite 600
Chicago, IL 60611, USA

Adrian C. Borges

Medizinische Klinik für Kardiologie
und Angiologie, Campus Mitte
Charité – Universitätsmedizin
Schumannstr 20/21
10117 Berlin, Germany

Paolo G. Camici

Division of Clinical Sciences
Hammersmith Hospital
MRC Clinical Sciences Centre
London SW7 2AZ, UK

Rodolfo Citro

Cardiology Imaging Unit
San Luca Hospital
Via F Cammarota
Vallo della Lucania
Salerno 84048, Italy

Lauro Cortigiani

Cardiac Imaging Lab, Lucca Hospital
“Campo di Marte”
Via dell’Ospedale 238
55100 Lucca, Italy

Kwan Damon

Division of Cardiology,
Department of Medicine
San Francisco Veterans Affairs Hospital
University of California San Francisco
San Francisco, CA 94143-0214, USA

Maurizio Galderisi

Department of Clinical
and Experimental Medicine
Federico II University Hospital
Cardiology Unit
Via Sergio Pansini, 5
80131 Naples Italy

Ekkehard Grünig

Pulmonary Hypertension Unit
Department of Cardiology and
Pneumology
University Hospital Heidelberg
INF 410
69120 Heidelberg, Germany

Michael Henein

Cardiology Department
Heart Centre University Hospital
90185 Umea, Sweden

Patrizio Lancellotti

Department of Cardiology
University Hospital Sart Tilman
CHU Sart Tilman B35
4000 Liège, Belgium

Jorge Lowenstein

Cardiodiagnostic Department
Investigaciones Médicas
Viamonte 1871, CP 1056
Buenos Aires, Argentina

Thomas H. Marwick

University of Queensland
Princess Alexandra Hospital
Brisbane
Queensland 4000, Australia

Mark J. Monaghan

Department of Cardiology,
King's College Hospital
Denmark Hill
London SE5 9RS, UK

Jean-Luc Monin

Department of Cardiology
Assistance Publique-Hôpitaux de Paris
Henri Mondor Hospital
51 avenue De Lattre de Tassigny
94010 Créteil, France

Miodrag Ostojic

Cardiology Department
University of Belgrade
Belgrade Medical School
Koste Todorovica 8
11000 Belgrade, Serbia

Philippe Pibarot

Laval Hospital Research Center
Québec Heart Institute
Laval University
2725, Chemin Sainte-Foy
Québec, G1V-4G5, Canada

Luc A. Piérard

Department of Cardiology
University Hospital Sart Tilman B-35
4000 Liège, Belgium

Fabio Recchia

Scuola Superiore Sant'Anna
Piazza Martiri della Libertà 33
56127 Pisa, Italy

Fausto Rigo

Dipartimento Cardiovascolare
Ospedale Civile di Mestre
Via Ospedale
30170 Venezia (VE), Italy

Alberto San Román

Department of Cardiology
Instituto de Ciencias del
Corazón (ICOCOR),
Hospital Clínico
Ramón y Cajal, 3
47005 Valladolid, Spain

Nelson B. Schiller

Division of Cardiology
Department of Medicine, Box 0214
San Francisco Veterans Affairs Hospital
University of California San Francisco
San Francisco, CA 94143-0214, USA

Juerg Schwitter

University Hospital Zurich
Clinic of Cardiology and
Cardiac MR Center
Raemistrasse 100
CH-8091 Zurich, Switzerland

Rosa Sicari

Institute of Clinical Physiology
CNR
Via Moruzzi, 1
56124 Pisa, Italy

Jae-Kwan Song

Echo Laboratory, Asan Medical Center
Department of Pulmonary and
Critical Care Medicine,
Asan Medical Center, University of Ulsan
College of Medicine, 388-1,
Pungnap-2dong, Songpa-gu
Seoul, Republic of Korea

William Wijns

Cardiovascular Center
OLV Hospital, Moorselbaan 164
9300 Aalst, Belgium

Section 1

Basic Principles, Methodology and Pathophysiology

Stress Echocardiography: A Historical and Societal Perspective

1

Eugenio Picano

Like many scientific innovations, in the last 30 years stress echocardiography has evolved from the status of “promising technique,” embraced by a few enthusiastic supporters [1, 2] amid general skepticism [3], to “established technology” [4] accepted by the overwhelming majority of cardiologists [5], to finally play a pivotal role in general cardiology [6, 7] with specialty echocardiography guidelines [8, 9] (Fig. 1.1). An astounding increase in the amount of editorial space devoted to stress echocardiography in major journals and meetings testifies to its greater acceptance by cardiologists (Fig. 1.1) and to the progressive expansion of the diagnostic domain, from coronary artery disease to its currently increasing role in the characterization of cardiomyopathy and valvular heart disease patients [10] (Fig. 1.2). The growth of this technique can be schematically staged by decade, grossly corresponding to three major technological step-ups: its infancy, as a monodimensional approach only applied with exercise during the 1970s; adolescence, characterized by two-dimensional echocardiography technology also applied with pharmacological stresses in the 1980s; young adulthood, when the methodology was reshaped with the addition of coronary flow reserve to standard wall motion analysis; and full maturity today, with deployment of the technique in the clinical arena to minimize the iatrogenic, legal, and social burdens that accompany the use of complementary and competing ionizing techniques such as scintigraphy and multislice computed tomography (MSCT) (Fig. 1.3).

1.1

Dawn of the Stress Echocardiography Era: From Experimental Studies to the Monodimensional Approach

In 1935, Tennant and Wiggers showed that coronary occlusion resulted in almost instantaneous abnormality of wall motion [11]. Experimental studies performed some 40 years later with ultrasonic crystals [12] and two-dimensional echocardiography [13] on a canine model proved that during acute ischemia [12] and infarction [13] reductions in regional flow are closely mirrored by reductions in contractile function, setting the stage for the clinical use of ultrasonic methods in ischemic heart disease. The monodimensional (*M-mode*) technique

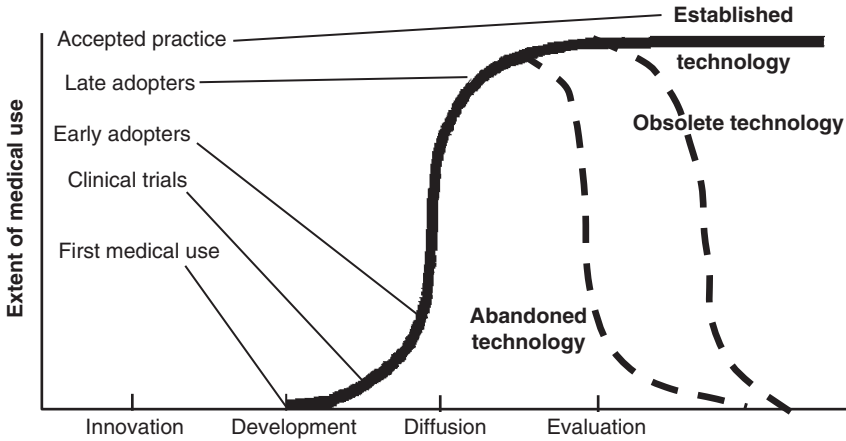


Fig. 1.1 The life cycle of a medical innovation, from promising technique (stress echocardiography in the 1980s) to established technology (stress echocardiography in the last 10 years). Various applications of stress echocardiography are all simultaneously present in today’s stress echocardiography laboratory, but at different stages of maturity. The qualitative assessment of regional wall motion abnormalities for detection of coronary artery disease is clearly “established”, but coronary flow reserve is still in the “early adopter” phase, while other applications (such as tissue characterization or myocardial velocity imaging with tissue Doppler or strain rate) have been discarded after the validation process and are now obsolete or have been abandoned for current clinical applications of stress echocardiography

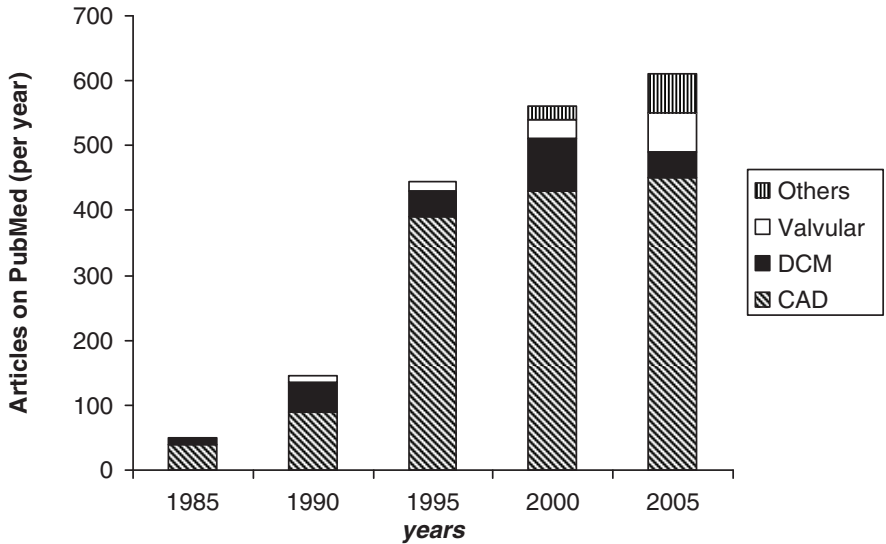


Fig. 1.2 Stress echocardiography vital signs: the editorial golden age. *y-axis* indicates the number of published articles on stress echo; the *x-axis* indicates the year. DCM=dilated cardiomyopathy; CAD=coronary artery disease (From Medline Healthgate)

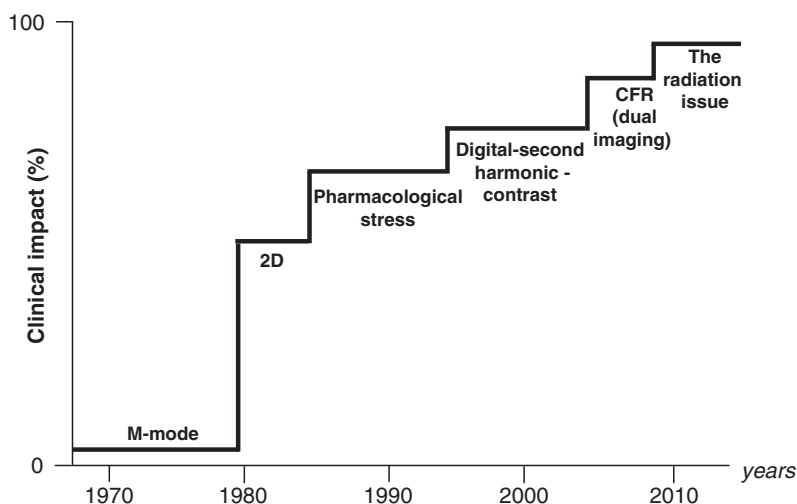


Fig. 1.3 The timeline of innovation in stress echocardiography. Quantum leaps in clinical impact are linked to technological improvements and cultural advancement. CFR = coronary flow reserve

was the only one available to cardiologists in the 1970s and nowadays appears largely inadequate for providing quality information when diagnosing myocardial ischemia. The time-motion technique sampling, according to an “ice-pick” view, greatly limited exploration to a small region on the left ventricle. Although this feature could hardly be reconciled with the strict regional nature of acute and chronic manifestations of ischemic heart disease, for the first time the monodimensional technique outlined echocardiography’s potential in diagnosing transient ischemia. The very first reports describing echocardiographic changes during ischemia dealt with the use of *M-mode* in two different models of exercise-induced ischemia [14] and spontaneous vasospastic angina [15]. Landmark studies by Alessandro Distante of the Pisa echo laboratory recognized transient dyssynergy to be an early, sensitive, specific marker of transient ischemia, clearly more accurate than electrocardiogram (ECG) changes and pain (Fig. 1.4). The potential clinical impact of these observations became more obvious with the advent of the two-dimensional technique, which allowed exploration of all segments of the left ventricle with excellent spatial and temporal resolution, and was, therefore, ideally suited for searching for the regional and transient manifestations of myocardial ischemia. If the monodimensional technique was a bludgeon, then the two-dimensional technique was a bow – a more potent weapon, and much easier to use.

1.2

Second-Generation Stress Echocardiography: Pharmacological Stresses in the 2D Era

Once armed with the bow – the 2D technique – stress echocardiographers now had to find the arrows – the proper stresses. Exercise, although already on hand, was soon revealed to be a blunt arrow: what was the “mother of all tests” for the cardiologist was

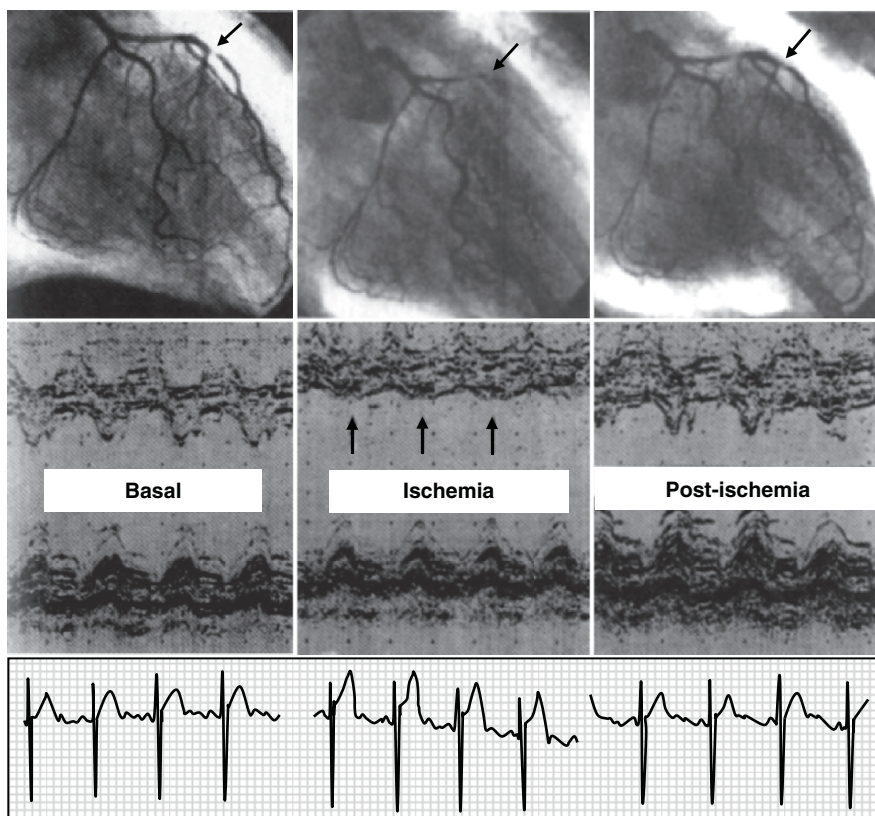


Fig. 1.4 Coronary angiographic (*upper panels*) and echocardiographic monodimensional tracings (*lower panels*) during attacks of variant angina induced by ergonovine maleate. At baseline, left anterior descending coronary artery shows a tight stenosis (*left panel*); the artery is totally occluded by a complete vasospasm during ischemia (*middle panel*); and it is again open in the recovery phase (*right panel*). The corresponding three frames of an original M-mode recording document a fully reversible sequence of myocardial ischemia. The septum moves normally at rest (*left panel*) and is obviously akinetic during ischemia (*middle panel*). During the recovery phase (*right panel*), the previously ischemic wall exhibits a significant overshoot in motion and systolic thickening. (From [15])

at that time a disagreeable “stepmother” for the echocardiographer due to the technical difficulties and degraded quality of echocardiographic imaging during exercise. The problem was minimized with posttreadmill imaging, still the standard in the USA today [16]. An alternative approach, more popular in Europe, was the introduction of pharmacological stress echocardiography detecting myocardial ischemia [17] and viability [18].

In the late 1980s, multiple generations of ultrasound equipment evolved very rapidly, boosting image quality and offering the ability to image almost any patient. In two-dimensional exercise echocardiography, stress echocardiography sometimes was a “guess gram” (Fig. 1.5) and torture for the eyes. It was often repeated by eminent opinion leaders that you needed “magic eyes” and “magic machines” to obtain good results. The technique divided the echocardiographic community into two camps, “believers” and “skeptics”

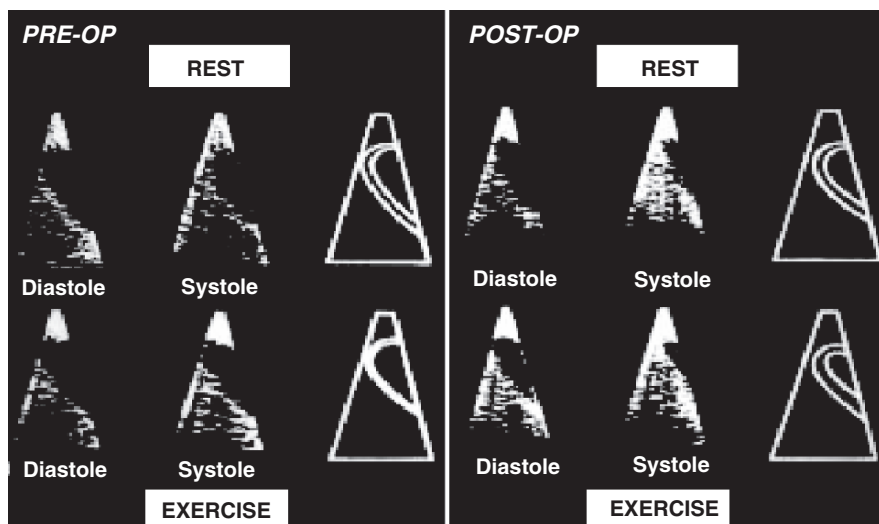


Fig. 1.5 Stress echocardiography in its infancy: not easy on the eyes. Exercise echocardiograms are shown before (*left panel*) and after (*right panel*) coronary artery bypass surgery. At that time (1979), image quality was so poor that even obtaining a single “typical example” for publication purposes was a challenge. (From [16])

[3, 4], and never attained extensive clinical application. Things changed rapidly in the mid-1980s, with the evolution of imaging technology and the advent of pharmacological stresses, which were less technically challenging than exercise. In the 1990s, thanks to this methodological evolution, the technique was upgraded from research toy to clinical tool. The widespread use of this technique received wide-scale support and credibility; prospective multicenter studies provided effectiveness [19] and safety [20] data with pharmacological stress echocardiography. The same groups that proposed stress echocardiography in journals and meetings now introduced the technique into their clinical practice. Rather than the number of published articles, it was this compelling argument that convinced most laboratories to implement stress echocardiography in their own practice as well; the world described in journals eventually came to resemble real-life cardiology (Fig. 1.6).

1.3

Third-Generation Stress Echocardiography Today: Coronary Flow Reserve and Dual Imaging

For 20 years, throughout the 1980s and the 1990s, stress echocardiography remained virtually unchanged [1, 4, 5]. Certainly, there were obvious, continuous, subtle improvements in imaging technology. Digital echocardiographic techniques permitted the capture and synchronized display of the same view at different stages. The introduction of native tissue harmonic imaging, which increases lateral resolution and signal-to-noise ratio, clearly improved endocardial border detection. Intravenous contrast echocardiography with second-generation lung-crossing agents for endocardial border recognition allowed

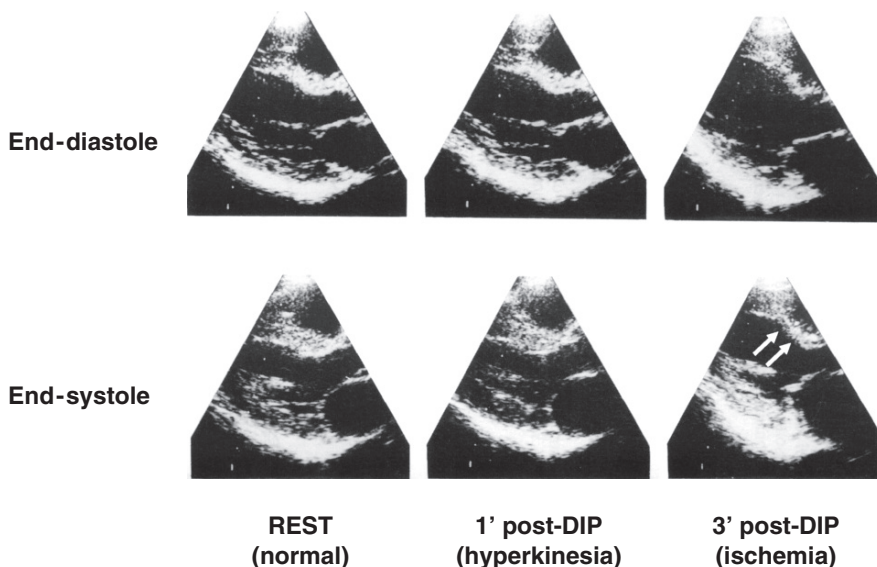


Fig. 1.6 The birth of pharmacological stress echo. End-diastolic (*upper panels*) and end-systolic (*lower panels*) frames at baseline (*left panel*), during early hyperkinetic phase (*middle panel*, 1 min postdipyridamole infusion), and 3 min postdipyridamole infusion at peak ischemic effect (*right panel*) showing septal akinesia. The quality of the image (compared to Fig. 1.5) is dramatically improved thanks to the evolution of technology and the use of pharmacological instead of posttreadmill exercise echo. (Original images from [17])

cardiologists to study otherwise “acoustically hostile” patients and segments [8, 9]. To be honest, however, the last 20 years were also disappointing with regard to the three great unfulfilled promises of stress echocardiography: tissue characterization of the myocardial structure (scar vs. normal tissue); myocardial perfusion with myocardial contrast echocardiography (allowing perfusion to be coupled with function in the same stress); regional wall motion quantification with myocardial velocity imaging methods (turning the diagnosis of regional wall motion from an opinion into a quantifiable unit). At first, each of these targets appeared to be within reach, based on strong experimental data and encouraging clinical experiences, but they did not pass the test of multicenter studies and to date have not revealed any valuable clinic impact [8, 9]. Each of these objectives – tissue structure, myocardial perfusion, and regional function quantification – can be realized in a more effective and reproducible way with cardiovascular magnetic resonance (CMR) – with delayed contrast enhancement for scar detection, contrast imaging for myocardial perfusion, and tagging for wall motion objective quantification [5]. However, in the last 5 years, a major innovation changed the face and the diagnostic content of stress echocardiography: dual imaging of wall motion and coronary flow reserve with pulsed-Doppler imaging of the midistal left anterior descending coronary artery [21–23]. Imaging coronary flow reserve dramatically expands the prognostic potential of stress echocardiography, since in the absence of wall motion negativity, the patient subset with reduced coronary flow reserve has a less benign outcome and in patients with wall motion abnormality, those with reduced coronary flow reserve also have a more malignant prognosis (Fig. 1.7) [22, 23]. In the same

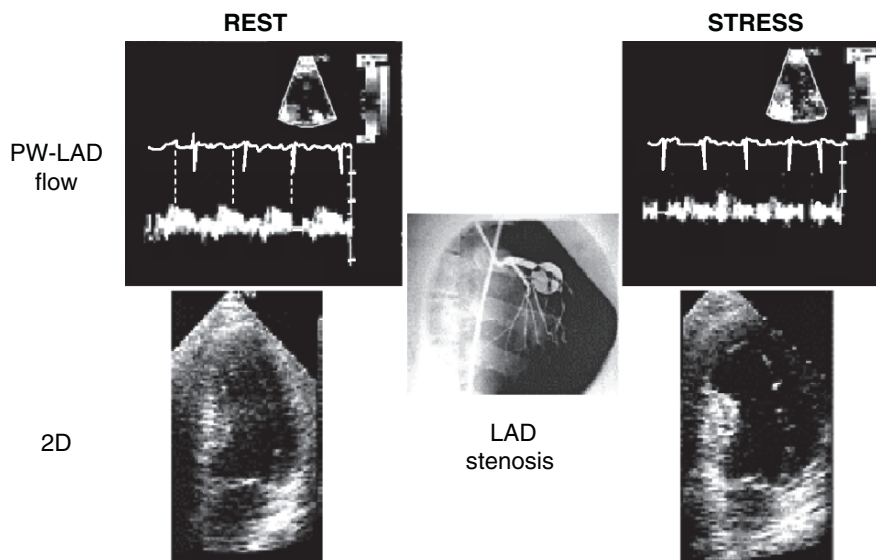


Fig. 1.7 The magical world of coronary flow reserve enters the stress echocardiography laboratory with pulsed Doppler, which allows assessment of coronary flow reserve on the middistal left anterior descending artery (visualized by color Doppler on *upper panel*). In this case, there is a normal coronary flow reserve, with a >2.5 -fold increase in coronary flow velocity during stress (*right lower panel*) compared with rest (*left lower panel*). LAD, left anterior descending; PW, Pulsed Wave Doppler. (By courtesy of Fausto Rigo, Venice-Mestre [21])

setting, with the same stress, it is now possible to image function and flow simultaneously, and therefore catch two “birds” (flow and function) with one “stone” (vasodilator stress). Although coronary flow reserve is a technology-in-progress and has yet to reach its full maturity, it is now considered a new standard in the clinical application of stress echocardiography [24]. However, once again this quantum leap in the impact of stress echocardiography was the result of a conceptual rather than a technological step-up during the last 5 years: that is, the need to incorporate long-term radiation risk in the risk–benefit assessment of competing imaging techniques [5]. Medical, legal, and social arguments have boosted the use of stress echocardiography as the best way to optimize the risk–benefit ratio for the individual patient, minimize the risk of litigation due to unjustified long-term cancer risk, and nullify the oncological population burden of cardiac stress testing [5].

1.4 Cardiac Imaging and Its Guidelines

After 30 years of evolution, in the last 10 years stress echocardiography has reached its established rank in the diagnosis and prognosis of coronary artery disease, as officially certified by general cardiology [6, 7] and specialist guidelines [8, 9]. These guidelines unanimously conclude that nuclear cardiology and stress echocardiography provide

comparable information on key issues such as diagnostic accuracy for noninvasive detection of coronary artery disease, identification of myocardial viability, and prognostic stratification. In the recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines, the advantages listed for stress echocardiography include higher specificity, versatility, greater convenience, and lower cost. The advantages of stress perfusion imaging include higher technical success rate, higher sensitivity (especially for single-vessel disease involving the left circumflex artery), better accuracy when multiple resting left ventricular wall motion abnormalities are present, and a more extensive database in evaluation of the prognosis [6]. The European Society of Cardiology guidelines (2006) on stable angina conclude that “on the whole, stress echocardiography and stress perfusion scintigraphy, whether using exercise or pharmacological stress (inotropic or vasodilation), have very similar applications” [7]. However, the certified, comparable clinical performance cannot be construed as an argument for an opinion-driven choice of one technique over the other. The ACC /AHA Task Force (Committee on Management of Patients with Chronic Stable Angina) concluded that “the choice of which test to perform depends on issues of local expertise, available facilities and considerations of cost-effectiveness” [6]. The European Society of Cardiology concluded that “the choice as to which test is employed depends largely on local facilities and expertise.” In the present era characterized by a quest for sustainability, the issues of relative cost (Fig. 1.8) [25], biological risk, and

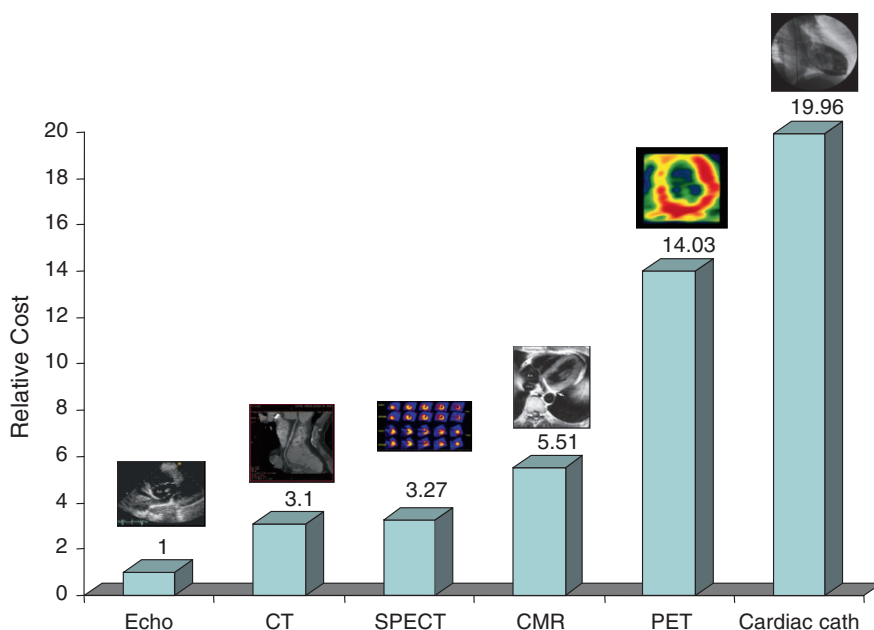


Fig. 1.8 Relative costs of cardiac imaging. CT=cardiac tomography; SPECT=single photon emission computed tomography; CMR=cardiac magnetic resonance; PET=positron emission tomography (Adapted and modified from [25])

environmental impact of stress-testing procedures – not even mentioned in the guidelines – should be included in the decision-making process, not only for cardiac stress testing, but for every imaging test in all branches of medicine, as clearly recommended by the European Commission Medical Imaging guidelines [26].

1.5 Cardiac Imaging and the Radiation-Induced Biorisks

Small individual risks multiplied by billions of examinations become significant population risks [27–31]. At least 10% of all cancers are due to diagnostic imaging, and at least half of them come from cardiac examinations (Fig. 1.9). Cardiac stress imaging contributes to these individual and population biorisks. On the individual level, the effective dose is expressed in millisievert (mSv). It provides an estimate of the whole-body dose and a measure of the biological effects. The dose of a single nuclear cardiology procedure ranges from 27 mSv (>1,500 chest X-rays) from a thallium scan to 10 mSv (500 chest X-rays) from a technetium-MIBI scan [32–34]. One millisievert corresponds to the dose equivalent of 50 chest X-rays (single postero–anterior projection = 0.02 mSv). According to the latest estimation of BEIR VII (2006), this exposure dose corresponds to an extra-lifetime risk of cancer per examination ranging from 1 in 500 (thallium) to 1 in 1,000 (sestamibi) [35, 36]. The typical effective dose of several common diagnostic procedures is reported in Table 1.1

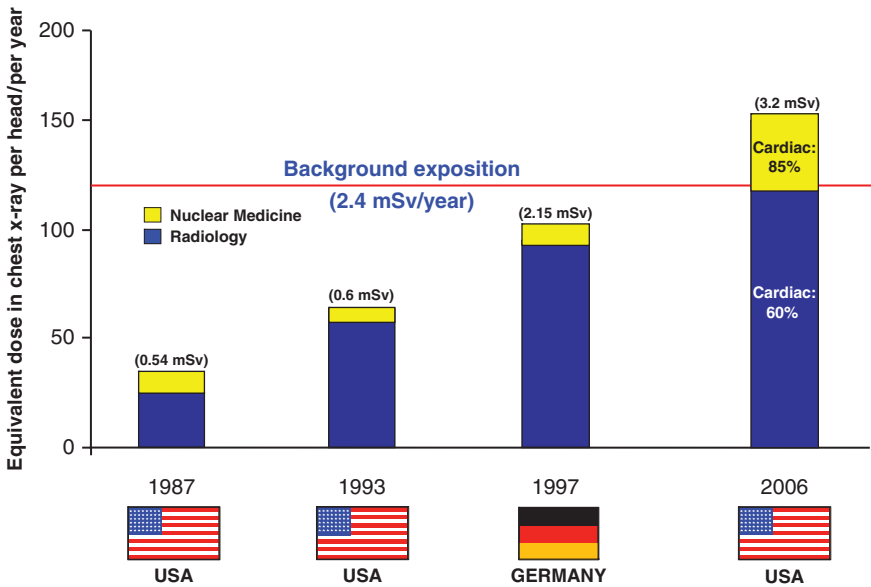


Fig. 1.9 Annual effective dose received by an average US inhabitant (from [23], National Council on Radiation Protection and Measurements). The total dose is of 3.2 mSv per year: 2.4 mSv from natural and 0.4 mSv from man-made sources. (Updated from [27])