Stress Echocardiography: A Historical and Societal Perspective

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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

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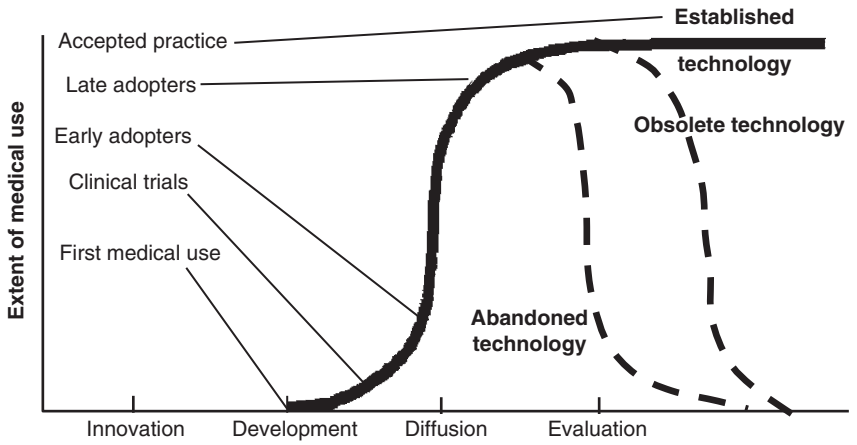

Fig. 1.1 The life cycle of a medical innovation, from promising technique (stress echocardiography in the 1980s) to established technology (stress echocardiography in the last 10 years). Various applications of stress echocardiography are all simultaneously present in today's stress echocardiography 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

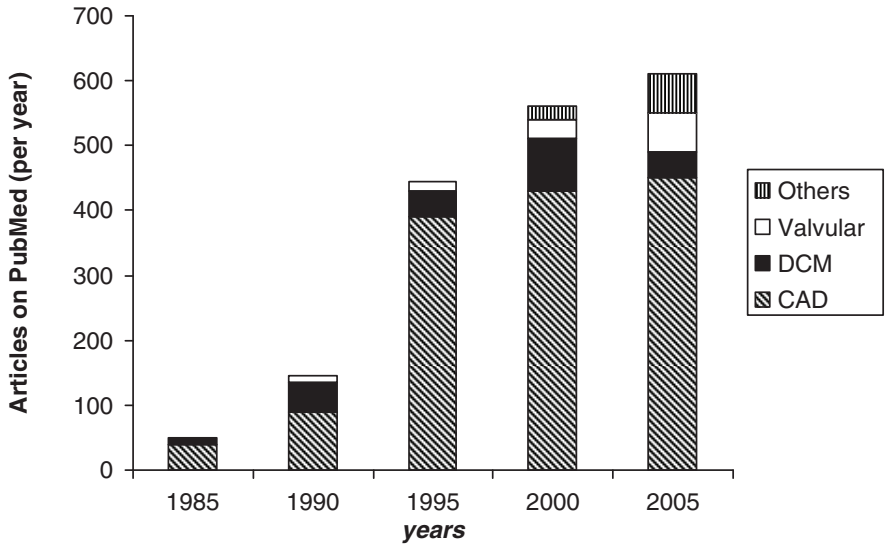

Fig. 1.2 Stress echocardiography vital signs: the editorial golden age. *y-axis* indicates the number of published articles on stress echo; the *x-axis* indicates the year. DCM = dilated cardiomyopathy; CAD = coronary artery disease (From Medline Healthgate)

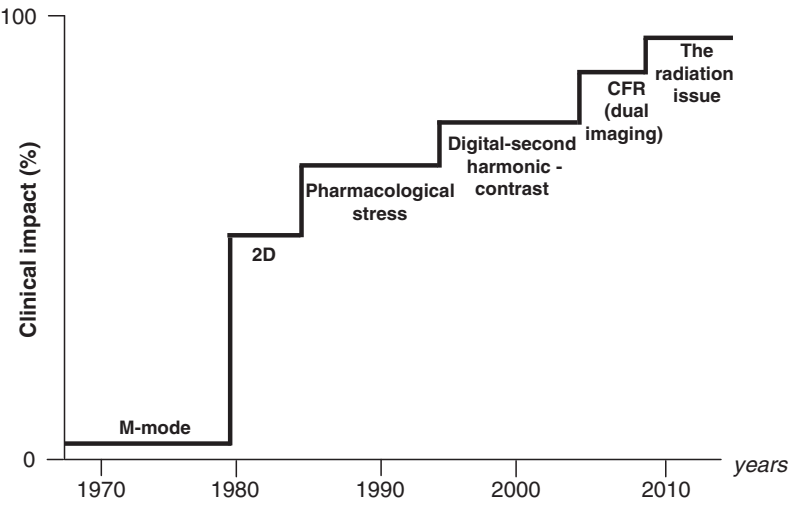

Fig. 1.3 The timeline of innovation in stress echocardiography. Quantum leaps in clinical impact are linked to technological improvements and cultural advancement. CFR = coronary flow reserve

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

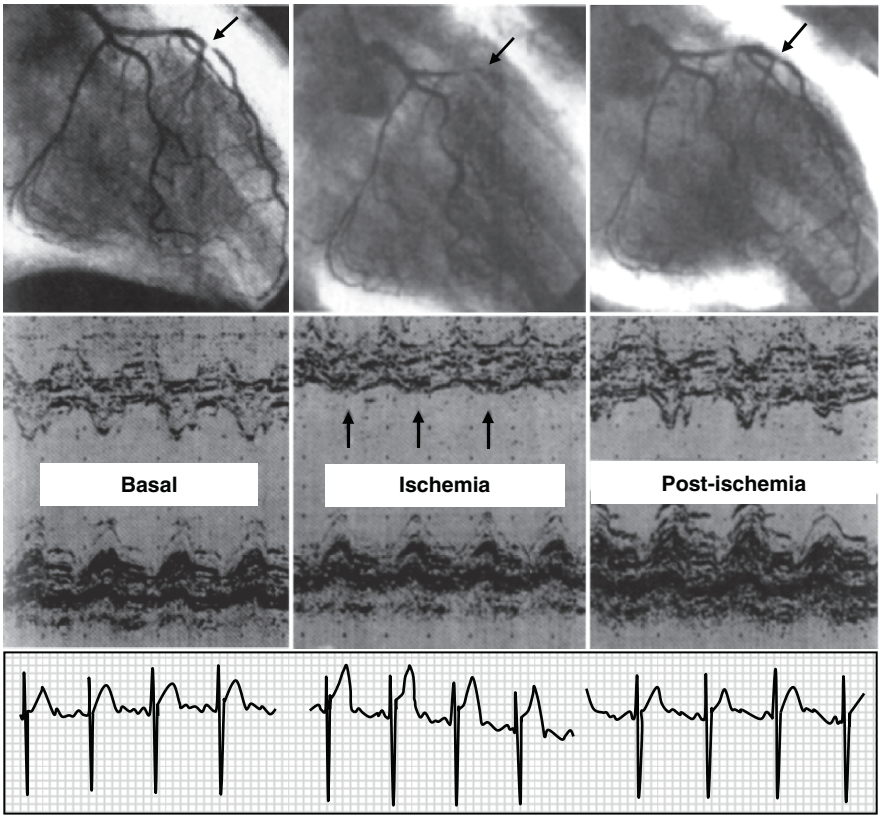

Fig. 1.4 Coronary angiographic (*upper panels*) and echocardiographic monodimensional tracings (*lower panels*) during attacks of variant angina induced by ergonovine maleate. At baseline, left anterior descending coronary artery shows a tight stenosis (*left panel*); the artery is totally occluded by 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"

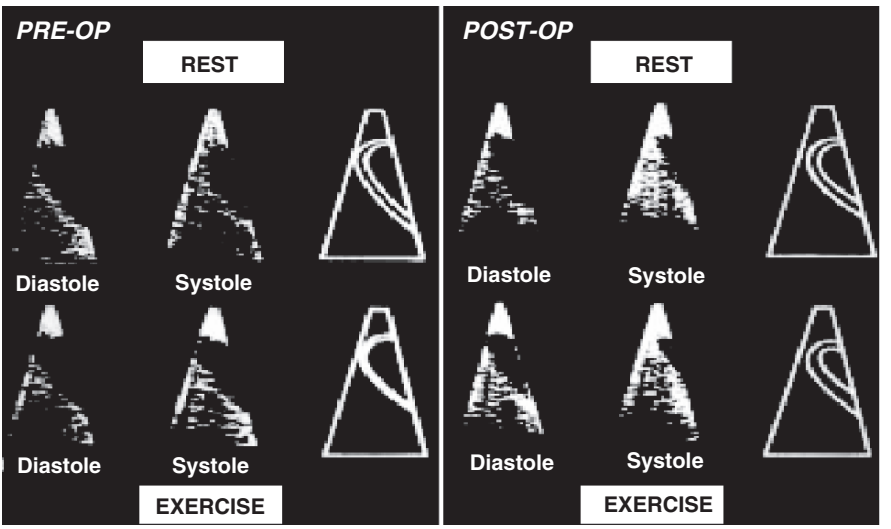

Fig. 1.5 Stress echocardiography in its infancy: not easy on the eyes. Exercise echocardiograms are shown before (*left panel*) and after (*right panel*) coronary artery bypass surgery. At that time (1979), image quality was so poor that even obtaining a single "typical example" for publication purposes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

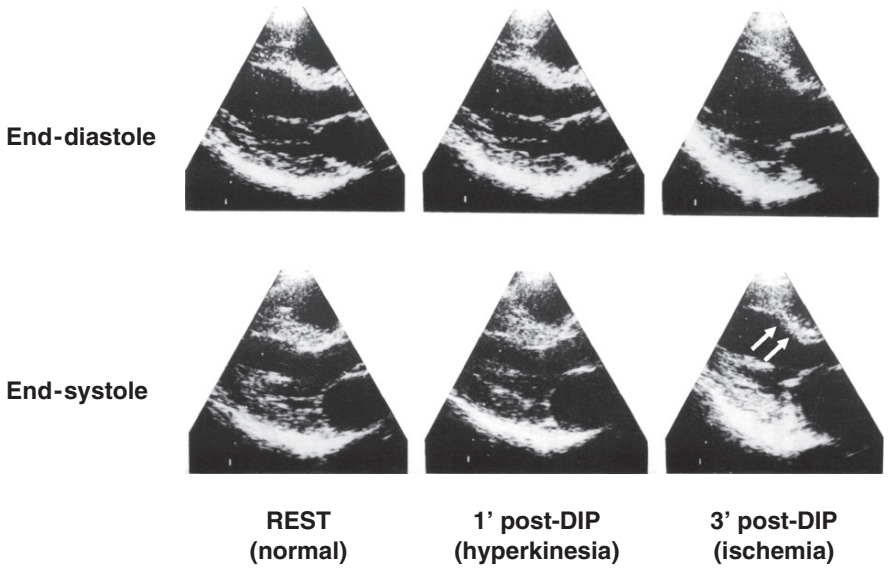

Fig. 1.6 The birth of pharmacological stress echo. End-diastolic (*upper panels*) and end-systolic (*lower panels*) frames at baseline (*left panel*), during early hyperkinetic phase (*middle panel*, 1 min postdipyridamole infusion), and 3 min postdipyridamole infusion at peak ischemic effect (*right 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 middistal 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

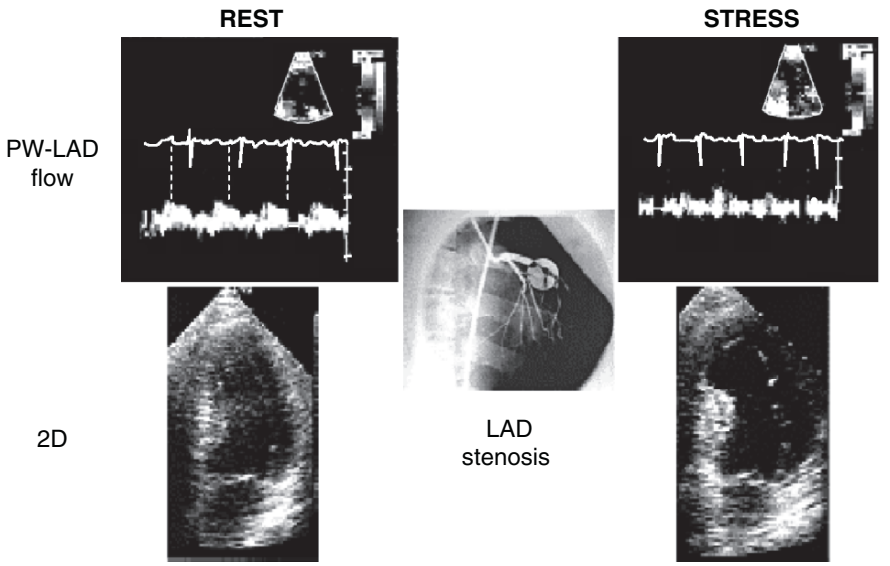

Fig. 1.7 The magical world of coronary flow reserve enters the stress echocardiography laboratory with pulsed Doppler, which allows assessment of coronary flow reserve on the middistal left anterior descending artery (visualized by color Doppler on *upper panel*). In this case, there is a normal coronary 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

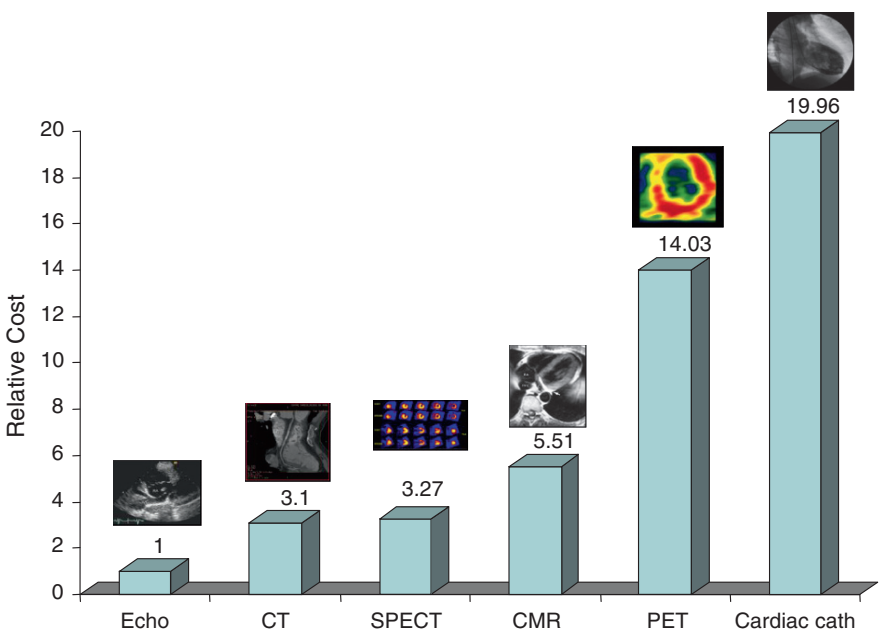

Fig. 1.8 Relative costs of cardiac imaging. CT = cardiac tomography; SPECT = single photon emission computed tomography; CMR = cardiac magnetic resonance; PET = positron emission tomography (Adapted and modified from [25])

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

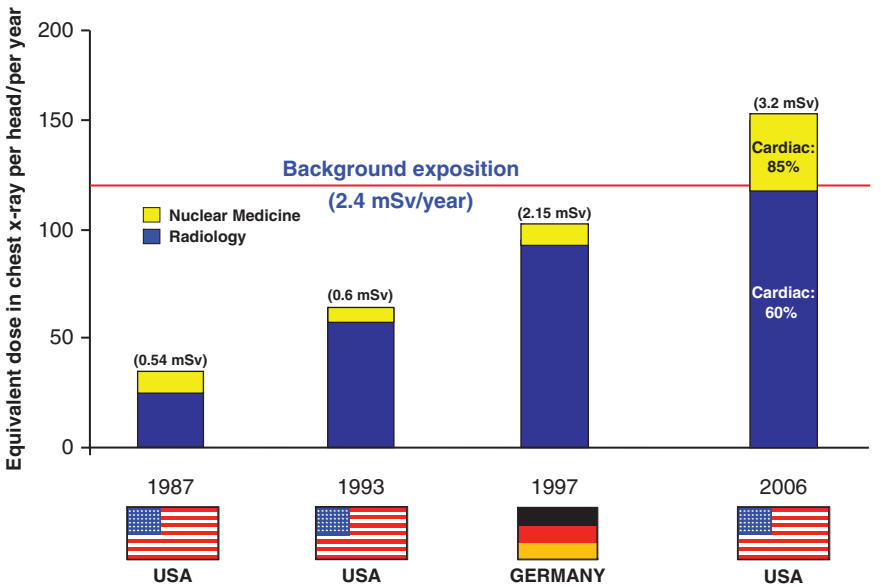

Fig. 1.9 Annual effective dose received by an average US inhabitant (from [23], National Council on Radiation Protection and Measurements). The total dose is of 3.2 mSv per year: 2.4 mSv from natural and 0.4 mSv from man-made sources. (Updated from [27])

Table 1.1 Doses in cardiology

Examination	Effective dose (mSv)	Equivalent no. of chest X-rays
Conventional radiology		
■ Chest X-ray (single postero–anterior)	0.02	1
Nuclear medicine		
■ Tc-99 m tetrafosmin cardiac rest–stress (10 mCi + 30 mCi)[a]	10.6	530
■ Tc-99 m sestamibi cardiac 1-day rest–stress (10 mCi + 30 mCi)[a]	12	600
■ Tc-99 m sestamibi cardiac 2-day stress–rest (30 mCi + 30 mCi)[a]	17.5	775
■ Tl-201 cardiac stress and reinjection (3.0 mCi + 1.0 mCi)[a]	25	1,250
■ Dual isotope cardiac (3.0 mCi Tl201 + 30 mCi Tc-99 m)[a]	27	1,350
64-Slice *Cardiac computed tomography*		
■ ECG pulsing, no aorta[b]	9	450
■ No ECG pulsing, yes aorta[b]	29	1,450
Interventional radiology		
■ Conventional rhythm device[c]	1.4	70
■ Cardiac resynchronization device[c]	5.5	275
■ Cerebral angiography[c]	1.6–10.6	80–530
■ Coronary angiography[c]	3.1–10.6	155–555
■ Abdominal angiography[c]	6–23	300–1,150
■ Peripheral angiography[c]	2.7–14	135–700
■ Coronary angioplasty[c]	6.8–28.9	340–1,445
■ Peripheral angioplasty[c]	10–12	500–600
■ Radiofrequency ablation[c]	17–25	850–1,250
■ Valvuloplasty[c]	29	1,450

[a] From [26], [33]
[b] From [34]
[c] From [35]
CT protocols that rescan the same region of interest (e.g., noncontrast and contrast-enhanced scans) impart two to three times the radiation dose

and translated into the corresponding additional lifetime risk of cancer per examination in Fig. 1.10 [35, 36]. The risk is cumulative, and the dose exposure of an average adult cardiology patient easily reaches 100 mSv, corresponding to 5,000 chest X-rays and an additional risk of 1 cancer in 100 [37]. This threshold can be reached, for instance, by summing up dose exposures of four thallium or dual isotope stress perfusion scintigraphy studies – still the preferred protocol for radionuclide stress imaging in the USA in spite of the unfavorable dosimetry [33, 35]. With the current best (BEIR VII) risk estimates, the 10 million stress perfusion studies per year lead to an estimated 20,000 new cancers each year in the USA alone (Table 1.2). The estimated 10 million cardiac CT studies per year yield an

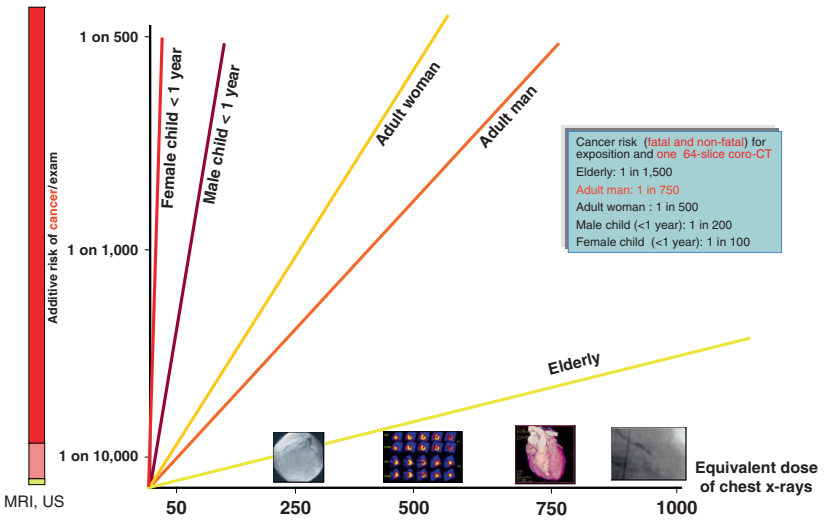

Fig. 1.10 Population risk of radiation-induced cancer, today around 10% of all cancers and still rising. (From [29])

Table 1.2 Cardiac imaging for detection of coronary artery disease: population impact

	Dose per examination (CXRs)	Risk per examination	Examinations per year	New cancers per year
MPI	1,000 (500–1,500)	1 in 500	10 million	20,000
MSCT	750 (500–1,500)	1 in 750	10 million	15,000
CMR	0	0	10 million	0
Stress echocardiography	0	0	10 million	0

CXR, chest X-ray; *MPI*, myocardial perfusion imaging; *MSCT*, multislice computed tomography; *CMR*, cardiovascular magnetic resonance

additional 15,000 new cancers per year in the USA alone (Fig. 1.11) [30]. Obviously this has raised public health concerns in regulating bodies and scientific societies. As stated in the recent White Paper of the ACR (American College of Radiology), "the expanding use of imaging modalities using ionizing radiation may eventually result in an increased incidence of cancer in the exposed population" [31]. If stress echocardiography and CMR are employed instead of perfusion imaging and MSCT, no known individual or population oncological burden is observed (Table 1.2).

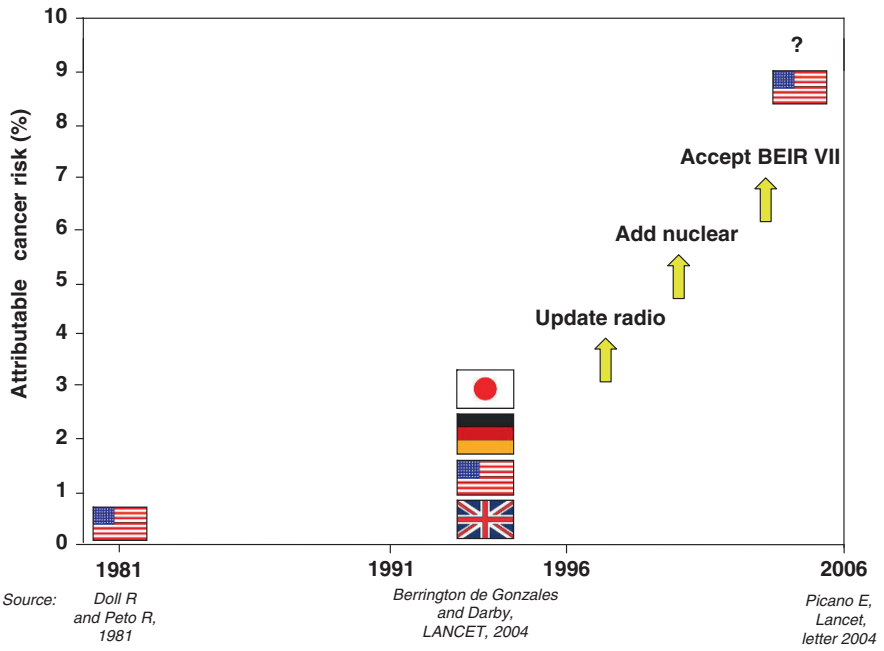

Fig. 1.11 Simplified effective dose ranges of some common medical procedures involving exposure to ionizing radiations in diagnostic nuclear medicine and radiological procedures. The reference unit is one chest X-ray (postero–anterior projection), equal to an effective dose of 0.02 mSv. There is a linear relationship between dose (*x*-axis) and risk (*y*-axis), with no safe dose (the risk line starts from zero). Ultrasound and MRI have zero dose and zero risk. (Adapted from [32])

1.6 Cardiac Imaging and the Regulatory Framework

The abovementioned environmental, population, and biological burdens are fully acceptable when there is no substitute or alternative for information provided by the imaging technique, in a proper risk–benefit assessment that includes long-term risks in the balance. The same burden may become too heavy, and the risks offset the benefits, when comparable diagnostic information can be obtained using widely available alternative techniques, with no known biohazards and no environmental impact. In cardiology, the frequent need for serial repeated stress imaging testing in the same patient amplifies the biohazard, since radiological risk is cumulative [38]. These obvious considerations have left a mark on the regulatory framework governing the use of cardiac imaging in medical guidelines, and – at least in Europe – in federal, national, and regional laws regulating cardiac imaging prescriptions. In the European Union [39], a 97/43 EURATOM

directive establishes that indication and execution of diagnostic procedures should follow three basic principles: the justification principle (article 3: "if an exposure cannot be justified, it should be prohibited"), the optimization principle (article 4: "according to the ALARA principle, all doses due to medical exposures must be kept As Low As Reasonably Achievable"), and the responsibility principle (article 5: "both the referring physician ordering the test – the prescriber – and the physician – the practitioner – are responsible for the justification of the test exposing the patient to ionizing radiations"). These principles have been reinforced on the national level. In Italy [40], a recent law (DL 187, 26 May 2000) states that an ionizing examination can only be performed when "it cannot be replaced by other techniques which do not employ ionizing radiation." In the same law, article 14 sanctions the inappropriate use of ionizing tests with fines up to €5,000 and jail for a period up to 3 months. These laws are not so strictly implemented in clinical practice, where at least 1 out of 3 imaging tests is inappropriate [41, 42] and both doctors [43–46] and patients [46] are largely unaware of doses and risks, setting the stage for a perfect medicolegal storm [38].

1.7 Cardiac Imaging in the Age of Sustainability: The "Eco-Eco-Echo" Diagnosis

In today's cost-environment – and risk-conscious climate, the prescribing physician must be aware that his/her choice places economic and biohazard burdens upon the planet, society, and the individual. Ours was the last generation of prescribers and practitioners that could afford to neglect costs and environmental impact, ignore radiological doses, and deny the risks of our often inappropriate imaging testing. Society, the government, patients, and the law will rightfully demand accountability for our acts. It is entirely likely that our increased awareness of the doses, risks, and environmental impact of imaging methods will profoundly reshape the way cardiology (and medicine in general) is taught, learned, and practiced. A cost-environment – and risk-conscious algorithm should follow simple rules. Faced with comparable or largely similar information, non-ionizing testing should be chosen: echo instead of nuclear, and MRI instead of CT. For any given ionizing test, the one with a lower dose should be chosen. For similar doses and accuracy, the test with less environmental impact should be chosen [for instance, CT rather than positron emission tomography (PET)]. This simple, common sense-driven algorithm could revolutionize the current practice of medicine. Today, the cardiac imaging community is gratified by the huge rise of imaging numbers, on the order of magnitude of +4,800% for CT, +2,800% for stress echocardiography, +100% for CMR, and +300% for stress perfusion imaging projected from 2006 to 2020 [47]. It does not matter that nearly half of these examinations [41, 42] are inappropriate – even when long-term risks are not considered [48].

In this societal perspective, sensitive to the environmental, economic, and societal milieu, a virtuous attempt to keep to the highest diagnostic standards while minimizing the economic and biological footprint of our medical acts will inevitably lead to a growing role for stress echocardiography in cardiac imaging practice.

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