REVIEW ARTICLE

Recent advances in cardiology

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Introduction

The past two decades have seen marked changes in the practice of modern medicine. There have been major technological advances in all fields which have dramatically altered traditional methods of diagnosis and have also had a profound effect on the therapeutics of many diseases. With the advent of newer drugs, previously untreatable conditions can, in many cases, be controlled. Epidemiological research has uncovered clues to various factors implicated in the aetiology of many diseases and in some instances a well established cause-effect relationship has been shown. Surgical management has also dramatically altered the course of many diseases.

Heart disease today remains the leading cause of death in the western world, and although advances have made changes in the ability to diagnose and treat cardiac disease, the problem still remains a major challenge (McGill, 1968; Kannel, McGee and Gordon, 1976). A breakthrough in the understanding of the primary aetiology of heart disease is still awaited and until then, the full armamentarium of diagnostic techniques and therapeutic possibilities is needed to manage patients with cardiovascular disease.

It is the aim of this review to outline, in part, some of the major advances in cardiology, focusing on the newer methods of diagnosis and treatment that have become available in recent years. It must, however, be stated that all of the techniques are meant to support rather than replace the most important diagnostic procedures—patient's history and physical examination.

The paper has been divided into the discussion of diagnostic, therapeutic and epidemiological factors which have found increasing use in the modern practice of cardiology today.

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Diagnostic techniques

Radiology

The time-honoured importance of the chest X-ray remains vital as an initial investigation of cardiac disease. Abnormalities in cardio-thoracic ratio still correlate highly with cardiac disease (Glover, Baxley and Dodge, 1973).

Advances in cine-radiography have allowed for higher quality coronary angiograms and left ventriculograms but the basic techniques are still those described by Judkin and Sones (Grossman, 1980; Braunwald, 1980b).

Recent advances in computer technology have played increasingly valuable roles in the refinement of angiographic images (Speller, 1981). Digitalization of radiological views has permitted more accurate assessment of cardiac parameters and subtraction of background shadows has enhanced the picture quality. As a result, both coronary lesions and ventricular wall abnormalities have been visualized more accurately (Krueger *et al.*, 1979).

Computer-assisted tomography (CAT) scanning has found some uses in cardiac diagnosis as improvements in scanning time from 6/sec to 2/sec have refined the pictures obtained. However, the constant motion of the heart provides a limitation to the microscopic accuracy of the CAT-scanner, and although both intracoronary and intracavitary lesions can be visualized, they have been analysed most effectively with other methods (Speller, 1981).

Reconstructions of images have been attempted in a three-dimensional model based on computer enhancement of multiple tomographic slices. This has been accomplished at the Mayo Clinic in America, and the device, called the Dynamic Spatial Reconstructor, is capable of creating a life-size 3-dimensional holographic image of all or any part of an internal organ (Gunby, 1980). Initial human studies have focused on the heart, lungs and blood vessels creating images capable of rendering accurate mea-

surements of heart muscle, blood content, cardiac indices, air content of lungs and the changes brought about by certain diseases.

Nuclear imaging and perfusion

There has been very rapid development and validation of radionuclide techniques as valuable non-invasive procedures for the diagnosis and assessment of many varied cardiac abnormalities. Prerequisite to these techniques has been the innovation and development of high performance gamma-scintillation cameras, as well as the computer equipment and software that permit rapid simplified data analysis. Also, newly developed radiopharmaceuticals have contributed to the widespread use and value of these tests.

Nuclear imaging has become an important adjunct in the diagnosis of myocardial infarction, especially in cases where classical parameters are equivocal. In the presence of a non-diagnostic electrocardiogram, confusing cardiac enzymes or an atypical history, a technetium-pyrophosphate scan may easily demonstrate a 'hot-spot' consistent with infarction. Alternatively, very early diagnosis has been made with thallium ('cold-spot') scans (Weisenberg and Schelbert, 1979). Thallium, a potassium analogue, has also found wide use in the non-acute assessment of cardiac ischaemia, both at rest and upon exertion combined with an exercise stress test. Both of the above described tests may be positive in a variety of cardiac disorders, but when combined with the proper history and investigations, have an 85% specificity for the presence of myocardial infarction and a 90% specificity for the presence of ischaemic heart disease (Bailey *et al.*, 1977).

Analysis of specific ventricular wall-motion abnormalities and accurate calculation of cardiac indices of volume, work and output has been achieved utilizing these radioactive tracers in blood-pool imaging and the development of sequencing techniques that permit a 'nuclear angiogram' to be generated by the computer. This has been accomplished by labelling the blood and then following either a bolus or tracer through the heart in its first pass or by studying specific regions of interest outlined by instructions given to the computer. Results have been obtained by these techniques which are as reliable and accurate as those obtained by an invasive cardiac catheterization and haemodynamic study, and have increasingly been used in the assessment of severity of ischaemic or valvular heart disease (Maddox *et al.*, 1978). Current recommendations regarding surgical decisions and long term prognosis of patients have been made using results from these nuclear assessments, and may in future spare patients the need for repeated invasive studies for the follow-up of certain

conditions. In some instances these procedures have become the evaluation of choice in critically ill patients who could not withstand a more invasive approach.

Electrophysiology

The ability to record intra-cavitary electrograms has greatly increased the understanding of cardiac electrical conduction and its abnormalities. Electrodes mounted on cardiac catheters, can be alternately used to stimulate or record from various parts of the cardiac chambers and sequential records can be made of the entire conduction system pathway (Grossman, 1980; Braunwald, 1980b). Tripolar or quadripolar catheters placed simultaneously in the atria, tricuspid orifice adjacent to the Bundle of His, coronary sinuses and apex of the ventricles have shown pathways of abnormal or anomalous conduction. The recorded signals differ from surface electrocardiograms in that they are filtered from frequencies between 40–500Hz where the intracavitary potentials are found, and can accurately record each phase of the activation sequence.

Utilization of electrophysiological techniques has permitted the accurate diagnosis of many complex arrhythmias including the sick sinus syndrome, supraventricular tachycardias, anomalous pathway re-entrant tachycardias and ventricular tachyarrhythmias (Pederson *et al.*, 1979). Mapping of arrhythmia origin in ventricular aneurysms has also been accomplished and has led to improvements in surgical excision of diseased tissue, resulting in fewer postoperative arrhythmias (Couch, 1959; Guiraudon *et al.*, 1978).

Further use of these procedures has been in the area of drug efficacy testing. Patients with known life-threatening arrhythmias can have them reproduced in the electrophysiology laboratory and challenged with one or more anti-arrhythmic drugs. Response to therapy can be observed and attempts to reproduce the arrhythmia by paced stimulation can assess the relative effectiveness of the drug in abolishing or moderating the arrhythmia (Mason and Winkle, 1980). In this way, patients with life-threatening arrhythmias may be accurately assessed as to their resistance to certain medication and specific tailoring of therapy can be individually accomplished. This may result in improved prognosis for long-term survival. The techniques of electrophysiological study have also found great usefulness in the precise analysis of many effects of newer anti-arrhythmic agents.

Endomyocardial biopsy

This technique has emerged as a valuable aid to

the diagnosis of many cardiac diseases. Before the development of a percutaneous approach, attempts to obtain heart tissue for histological study was a high risk and often life-threatening procedure which was seldom justified. In 1962, Konno and Sakakibara in Japan developed a biptome which could be introduced via a brachial vessel to obtain endocardial tissue with little morbidity and mortality (Sakakibara and Konno, 1962). Further modifications of this technique both in Britain and the United States have resulted in the development of both left and right heart biptomes which can be used percutaneously to obtain 3–4 mm samples of endomyocardium with negligible risk to the patient (Konno, Sekigushi and Sakakibara, 1971; Mason 1980; Richardson, 1974). The value of this procedure has been shown most conclusively in the recognition and management of cardiac allograft rejection and is the cornerstone on which diagnosis and treatment of this condition rests (Caves, 1974).

Increasingly widespread availability of this procedure has dramatically increased knowledge about many cardiac diseases and in some cases has determined their cause. Although the aetiology of many of the cardiomyopathies remains as yet unknown, some diagnoses have been made from the biopsy tissue, for example the cardiomyopathy associated with therapeutic agents including antineoplastic drugs, such as doxorubicin, alcohol, various infiltrative systemic diseases such as sarcoidosis, amyloidosis and haemochromatosis and occasionally with infectious agents which may include viruses, bacteria or fungi (Melvin and Mason, 1982).

There is also active research being carried out into the pathological changes induced in the myocardium by atherosclerotic, valvular heart disease and other causes of impaired ventricular function.

Echocardiography

A discussion of diagnostic aids in cardiology could not be complete without stressing the important role of echocardiography. In the past two decades this procedure has progressed to become one of the most valuable techniques in the practice of modern medicine. The evolution of two-dimensional echocardiography from the M-mode technique has improved dramatically the ability to diagnose many cardiac conditions. Both methods are based on the transmission of a short pulse of high frequency sound from a piezo-electric crystal which acts both as a transmitting and receiving unit. The sound wave travels in a direct path into the body reflecting a portion of its energy back to the transducer at each tissue interface. The device calibrates time between transmission and reception of the 'echo' into distance between the crystal and the interface. This is displayed on a

moving scale and additional brightness indicates the strength of the reflected signal. Thus, motion of heart tissue in a single plane can be assessed and various parts of the heart are studied depending on where the crystal is directed (Feigenbaum, 1976).

Two-dimensional echocardiography uses this same principle but uses multiple transducers or moves a single transducer through a plane of tissue, to examine more parts of the heart at once. A computer system freezes each single M-mode slice and lines it up in order, resulting in the presentation of a tomographic image of the heart as a frozen frame. These frames move rapidly with repeated transmission of the sound beams and create about 30 frames per second. Viewing the resulting image gives the appearance of watching the heart in motion and all or parts of the heart can be seen. It is important to note that with single dimensional (M-mode) pictures, the frequency response is much higher, (approximately 1000 frames/second), so that certain abnormalities of the heart are better assessed with M-mode scans. However, anatomic structures are more readily recognized on two-dimensional pictures and certain views can easily show cardiac pathology not apparent by the M-mode technique (Popp *et al.*, 1980). The result of these advances has been the remarkable ability to make accurate non-invasive assessments of a wide variety of cardiac disease that was previously assessed by either cardiac catheterization or not at all.

Two-dimensional echocardiography is of great value in the assessment of congenital heart disease with respect to the anatomical relationship of cardiac valves to chambers, inter-relations of the great arteries and other anatomical abnormalities. Injection of saline at rapid rates produces echo-visible microbubbles which can outline septal defects between atria or ventricles as well as document valvular insufficiency (Popp *et al.*, 1979; Popp *et al.*, 1980; Popp, 1980). Ventricular wall motion and chamber sizes can be used in the assessment of atherosclerotic heart disease as well as cardiomyopathies. Valve motion can be assessed and followed in rheumatic disease and vegetations may be seen in endocarditis. Tumours are often easily visible and echocardiography has become the principal diagnostic means of documenting atrial myxomas.

Certain cardiomyopathies have become quite well-recognized by echocardiography. Congestive cardiomyopathies have large globular, poorly contractile hearts. The ventricular wall thickness is near normal and the hypocontractility is uniform. Certain restrictive myopathies show good systolic function and may show endocardial echoes representing fibrosis, or in amyloidosis a thick myocardial wall, small cavity, and a uniform ground glass or scintillating set of echos in the myocardium (Fowles *et al.*, 1978). Hypertrophic cardiomyopathy may show asymme-

tric septal hypertrophy and/or systolic abnormalities of mitral valve motion.

Pericardial disease is diagnosed very accurately with both types of echocardiography. Effusion can be estimated, as can thickening of the pericardial surfaces but is not reliable for diagnosis of constrictive disease (Schnittger *et al.*, 1978).

Thus the advances in echocardiography have allowed for a wide application of this technique to all fields of cardiac disease. It is non-invasive, has a high yield of valuable information and often is precise enough to spare the patient further more risky, invasive and uncomfortable investigation.

Therapeutics

New techniques

Percutaneous transluminal coronary angioplasty (PTCA). In 1979, Gruntzig, Senning and Siegenthaler reported a dramatic new method of treatment of atherosclerotic coronary artery disease. They developed a catheter system introduced percutaneously as in cardiac catheterization, which was used to dilate stenotic arteries by controlled inflation of a distensible balloon within the catheter. Over the past three years this technique has proven to be a viable alternative to coronary bypass surgery in certain selected groups of patients.

The technique is based on cannulating the diseased vessel with the special catheter and then inflating the balloon at the site of the stenosis, thus effectively crushing the lesion, removing the stenosis and decreasing the coronary flow gradient. Pathological study of this technique has shown that the atherosclerotic plaque is not pushed into the vessel's media, but may break up and embolize in small fragments downstream which do not apparently compromise the viability of the myocardium. Patients are anticoagulated during and for 3–6 months after the procedure.

Two important caveats attend the use of this procedure. The first is that the lesions to be dilated must be in a position which is both reachable by the catheter and discrete (i.e. less than 1 cm in length and distant from a bifurcating branch vessel.) The second is that patients must be candidates for operation by conventional surgical coronary artery bypass as a result of disabling symptoms and clinical status. This is important in that an appreciable number of PTCA procedures result in deterioration in clinical status of the patients necessitating emergency bypass surgery for 6–7% of cases. This occurred in 10% of Gruntzig's initial study group but the incidence of complications requiring surgery has diminished in more recent reports (Gruntzig *et al.*, 1981; Cowley *et al.*, 1980).

Most reported failures of this technique are as a result of technical limitations caused by anatomical

factors but careful selection of patients has limited these poor results under optimal conditions. Instantaneous revascularization can be accomplished with a success rate of 64–80%. Follow-up of the original patient group indicated prolonged vessel patency and maintenance of improved clinical status in a high proportion of cases (Gruntzig *et al.*, 1981).

Nevertheless, it must be re-emphasized that this procedure, although of great potential benefit, is also attended by a significant potential morbidity and a small mortality of 2–3%, and is only appropriate for a small selected percentage of patients with atherosclerotic disease.

A further point concerning PTCA should be mentioned. Recently attempts have been made to reduce the extent of myocardial infarction size by very early interventions. Attempts have been made to lyse the thrombus to cause the acute event, by drugs such as streptokinase and urokinase. These will be described more fully in a subsequent section. However, it has also been demonstrated that PTCA can play a role here in limiting infarct size by destroying the thrombus with the balloon catheter. There is currently a trial under way in the United States to determine the value of PTCA as a technique for limitation of infarct size. It is obvious that the value of this technique is wholly dependent on getting the patient to hospital and into the catheter laboratory before the jeopardized tissue in the myocardium is irreversibly necrotic, and this factor may limit the usefulness of PTCA in this area.

Streptokinase in acute myocardial infarction

Attempts to limit the size and consequent damage resulting from transmural myocardial infarction have become increasingly common in the past few years. It has been recognized that the damage caused by an initial infarction has multiple both short and long-term sequelae that effect both the immediate prospects for patient survival and the later prognosis of the patient. It has been assumed that absolute reduction in size of any myocardial infarction would benefit patients in both these effects.

A controlled trial of intravenous streptokinase, a fibrinolytic agent, was carried out in eleven European centres on 315 patients and was designed to test the hypothesis that this drug would benefit patients with acute myocardial infarction with respect to their cardiac performance, limitation of infarct size and ultimately their survival (European Co-operative Study Group for Streptokinase Treatment, 1979; Editorial, 1979). The results indicated, in patients who were considered medium to high risk, based on age, vital signs, and arrhythmias, that there was a lower mortality in patients treated with streptokinase (15.6% v. 30.6% in the control group) at 6 months and

that risks of using the drug (2% morbidity and mortality) were less than risk of mortality. Further studies have shown the benefit of intracoronary streptokinase as a limiter of infarct size but acknowledge the need for a fully-equipped catheter laboratory and an available team to administer the drug (Rentrop, 1980). This may prove to be the limitation of this technique since it is not cost-effective to maintain such a facility in each hospital to which a patient with a myocardial infarction may be admitted. Additionally, this procedure is not of proven benefit in uncomplicated infarcts and thus may, at its current state of the art, only be appropriate for patients with complicated infarctions who may be transferred to facilities able to manage them more effectively (Sullivan, 1979).

Current recommendations do not advocate the routine use of streptokinase, and further multicentre trials both in Europe and America are under way to assess its role in the management of acute myocardial infarction.

Heart transplantation

Heart transplantation has been of proven value in therapy since 1967 and although world interest mounted and peaked in the early 1970s many centres have abandoned their transplant programmes as a result of high costs and high patient mortality.

However, work in the field has continued at Stanford University where the initial technical procedure was described in 1960, and ongoing laboratory and clinical research have resulted in dramatic successes by the transplant team there (Lower, Stoler and Shumway, 1961). Over 250 patients have received new hearts since 1968 with over 80 patients currently alive and well. Stanford's statistics reflect a steadily improving prognosis for their patients based on advances in immunology, drug therapy and rigid patient selection. Currently the patient selected for transplant must be aged 50 years or less with end-stage heart failure, no other systemic disease and a strong will to live. A patient may expect a 70% chance of survival in the first year with a gradual decline to 50–60% over the next five years (Baumgartner *et al.*, 1980; Hunt and Stinson, 1981). Recent advent of the drug cyclosporin A discovered in 1972, which limits immunosuppression selectively to the T-cell line, so vital to foreign tissue rejection, and allows more rapid wound healing, has improved patient management, decreased hospital stay, and has for the first time, allowed successful heart-lung transplantation to be carried out. There are currently 3 survivors of this latter procedure doing well as out-patients (Medical News, 1981). Other centres have continued work in the field and at present heart transplantation is carried out in five or six major centres in the world. It is

important to stress the need for any institution doing such work to have both the financial means and research facility to support the programme. As further advances in immunology are made it will become easier to manage the complications of infection and rejection in these patients and should further improve their ultimate prognosis. It is certain, at this time, that for severely disabled patients with end-stage heart disease and hopeless prognosis, heart transplantation is a viable life-saving procedure with the proven ability to return the patient to a near normal lifestyle.

New drug therapy

There is little doubt that the development of new pharmaceutical agents has dramatically altered the practice of modern cardiology. The past decade has seen the emergence of a whole new class of drugs including the betablockers, calcium antagonists and vasodilators which have made the treatment of all aspects of cardiac illness more effective. Research into the mechanisms of atherosclerosis has shed new light on the potential uses of antiplatelet agents and drugs affecting the prostaglandin metabolites (Braunwald, 1980a; Haft, 1979). These include aspirin, dipyridamole, many of the non-steroidal anti-inflammatory agents and possibly even sulphinpyrazone, a uricosuric agent whose use in patients surviving myocardial infarction has engendered tremendous controversy (The Anturane Reinfarction Trial Research Group, 1978, 1980; Kolato, 1980). As mentioned previously, fibrinolytic agents are being studied in acute myocardial infarction with the potential goal of limitation of infarct size and reduction of early and late morbidity and mortality. Vasodilator agents have been developed for both acute and chronic treatment of congestive failure and drugs such as sodium nitroprusside, hydralazine, prazosin and the new angiotensin-converting enzyme inhibitor, captopril, have been studied with encouraging results (Dzau *et al.*, 1980; Fitchett *et al.*, 1979; Colucci *et al.*, 1980). It is important to note that research into the effects of drugs on cardiovascular disease has also revealed certain agents implicated in the causation of illness. Elucidation of these mechanisms has led to a better understanding of certain conditions including the cardiomyopathies caused by the anthracyclin group of antineoplastic agents and alcoholic heart disease (Bristow *et al.*, 1978; Demakis *et al.*, 1974). Although there are many examples of the way in which the introduction of new drugs has altered and improved the practice of cardiology, it is pertinent to focus upon some of the major drug classes that are in current use.

The betablocker drugs have been in clinical use for over a decade, and research into their mode of action

has evolved steadily since their discovery in the 1940s. However, in addition to their well-known effectiveness in angina, hypertension and arrhythmia management, there has been recent interest in their role in prevention of mortality and sudden death, especially after myocardial infarction. Two major international studies, The Norwegian Multicentre Study Group (1981) using timolol and the NHLBI using propranolol have concluded that betablockers significantly reduce the risk of mortality and re-infarction in patients who survive acute myocardial infarction (Sleight, 1981; Braunwald, 1980a). This has major implications for all patients with atherosclerotic coronary disease and it may be that the coming years will see all coronary artery disease patients on betablockers, in an attempt to reduce the marked mortality of cardiovascular disease. Other research in the area of betablockers includes the possible limitation of infarct size in acute myocardial infarction, as well as development of cardioselective β_1 and β_2 agents, lipophilic agents and the promising advent of betablockers with intrinsic sympathomimetic activity (ISA) which may well limit many troublesome side effects attendant with the use of betablockers. Studies with one non-selective betablocker with ISA, pindolol, have shown that its partial agonist activity may replace the loss of resting sympathetic tone attendant with the use of betablockers, and this attenuates the fatigue and bradycardia produced by these agents (Aellig, 1981). This may allow safer use of these drugs in myocardial ischaemia and infarction, thus maximizing their effectiveness as potential agents for limitation of infarct size, treatment of angina and reduction in morbidity and mortality (Samek and Roskamm, 1981).

Increasing use of calcium antagonists has also resulted in the improved management of many cardiac problems, especially arrhythmias. These agents have a different mechanism of action from other conventional anti-arrhythmic drugs in that they affect a different channel in the action potential which is operative during the plateau phase of repolarization. These drugs have selective effects on specific cardiac tissue especially the sino-atrial and atrioventricular node, and also are specifically active against the smooth muscle cells of the vascular wall resulting in vasodilatation and abolition of coronary artery spasm. They are thus highly effective in the management of specific arrhythmias such as supra-ventricular tachycardia, atrial fibrillation (in controlling the ventricular rate) and are of proven benefit in the treatment of atypical/variant angina, coronary artery spasm and even typical angina pectoris (Antman *et al.*, 1980; Pepine and Conti, 1981). These agents although highly effective are also quite potent and have adverse effects which may include negative inotropy, chronotropy, conduction blocks and

orthostatic hypotension. The non-cardiac adverse effects are infrequent and include vertigo, headache, nervousness, pruritus and constipation (Schwartz, Keefe and Harrison, 1981).

The beneficial effects of vasodilator therapy on cardiovascular functions have been known since 1956 (Fitchett *et al.*, 1979; Judson, Hollandes and Wilkins, 1956). However, in recent years these drugs have become increasingly utilized as a mainstay in the effective treatment of hypertension, severe angina, advanced congestive heart failure and have become essential to the treatment of acute papillary muscle and ventricular septal rupture in myocardial infarction, valve regurgitation, as well as both ischaemic and non-ischaemic forms of cardiomyopathy (Mason, 1978).

The mode of action of these drugs is based upon the principal of reduction of ventricular preload and afterload by direct reduction of systemic and pulmonary vascular resistance. This results in decreases in intra-ventricular filling pressures, and improvement in cardiac output, with consequent improvement in the patient's functional class (Braunwald, 1980b; Mason, 1978). The direct action by these agents on the vasculature may be arterial, venous or both. Initial use of these agents concentrated on reduction of peripheral venous tone (preload) to relieve symptoms of congestion in the lungs in patients with left ventricular failure. Although afterload undoubtedly declined, the value of vasodilators as direct inhibitors of peripheral arterial resistance was not appreciated until some years later (Burch, Leon-Galindo and Cronvich, 1976). In the early 1970s with the advent of balloon counterpulsation, nitroprusside, nitrates and other agents, success was observed in the treatment of myocardial pump dysfunction secondary to myocardial infarction. Advantages of this therapy were also noted in the treatment of severe acute heart failure, chronic congestive heart failure and acute hypertensive emergencies, although there is currently a debate as to the potential for long-term benefit of such therapy in the chronic situation since it has been repeatedly shown that many patients become refractory to these agents over variable lengths of time (Chatterjee, Parmley and Lanz, 1973b; Chatterjee, Parmley and Swan, 1973a; Elkayam *et al.*, 1979; Packer *et al.*, 1982). It may be, however, that this tolerance is individualized to the patient and that certain drugs do not result in loss of their effect where others may. It cannot be predicted which agent will lose its effect in any one patient so that several drugs may have to be utilized in long-term management of such patients. More recently the introduction of newer agents including the angiotensin-converting enzyme inhibitor, captopril, has resulted in fewer episodes of intolerance and side effects. Captopril is thought to exert its effect by a competitive block of

the renin-angiotensin-aldosterone system which is thought to be responsible, in part, for the increased systemic vascular resistance in these patients. It is an effective oral agent and also has improved renal function in some settings, and may thus be a good choice for patients with severe cardiac failure complicated by azotaemia (Dzau *et al.*, 1980).

Some physicians feel that vasodilator therapy is only important as an adjunct in the treatment of severe heart failure when the traditional management with digitalis and diuretics has not been adequate. Another opinion is that these agents are equal or superior alternatives to conventional therapy. It is apparent, however, that a remarkable change of focus has occurred from emphasis on alteration of contractility to alteration of cardiac loading factors that primarily relax vascular smooth muscle without direct action on the heart. In both in-patient and out-patient treatment these modalities have provided promising new means of treating many forms of severe cardiovascular disease.

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