Drug-Induced Heart Failure

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Congestive heart failure (CHF) is a complex clinical syndrome that results from cardiac dysfunction (1). Signs and symptoms that are frequently encountered in patients suffering from CHF are dyspnea, fatigue, pulmonary crepitations and peripheral edema. Its clinical course is often characterized by periods of exacerbating symptoms, alternated with periods in which the patient experiences fewer or no symptoms. Epidemiologic studies indicate that both the prevalence and the incidence of CHF increase (2–4).

Congestive heart failure is predominantly caused by cardiovascular diseases, such as coronary artery disease, hypertension and valvular heart disease (3,5). However, in some patients the occurrence of CHF can be attributed to the cardiotoxic effect of a particular drug. Furthermore, as several categories of drugs may exert unfavorable hemodynamic effects, these drugs may act as a precipitating factor for a relapse in patients with previously compensated CHF. Pathophysiologically, CHF may result from drug-mediated effects on cardiac preload, cardiac afterload or myocardial contractility. Drugs that increase cardiac preload or cardiac afterload may have unfavorable effects on ventricular function, because increased cardiac preload or afterload intensifies the demand on ventricular performance. The ability of the heart to comply with this increased demand will depend on preexisting ventricular function. Drugs may also have a negative inotropic effect as a result of their direct cardiotoxic properties. Similarly, the likelihood of the occurrence of heart failure induced by cardiotoxic drugs may depend on preexisting ventricular function, although some drugs may have detrimental effects in patients with previously normal cardiac function. We will discuss the potential ability of several categories of drugs to induce or exacerbate heart failure.

CYTOSTATICS

Anthracyclines. The anthracyclines are effective antineoplastic agents which are used in the treatment of many types of malignancy. Daunorubicin and doxorubicin are among the most frequently used anthracyclines included in chemotherapeutic regimens (6). The anthracyclines are antibiotic agents which antineoplastic action results from the inhibition of the nucleic acid synthesis by binding to both strands of the deoxyribonucleic acid (DNA) helix. This binding prevents normal function of the ribonucleic acid (RNA) and DNA polymerases. The introduction of the anthracyclines has contributed considerably to the improvement of survival in patients with cancer. However, anthracycline-induced cardiotoxicity is a well-known adverse effect of this category of drugs and a major limitation to the total dose that can safely be administered (6). Cardiotoxicity is considered to be an adverse effect of all anthracyclines, although epirubicine may cause less cardiotoxicity as compared with doxorubicine (7). Formation of free oxygen radicals, disturbance of the mitochondrial energy metabolism and intracellular calcium...
of the patients with decreased fractional shortening at the end of the therapy still had decreased systolic function at long-term follow-up. In contrast, of patients with a normal echocardiogram at the end of therapy, only 12% (8/64) had decreased fractional shortening at long-term follow-up (p < 0.001). Patients suffering from anthracycline-induced cardiotoxicity may finally develop signs and symptoms of heart failure when impaired systolic function is unable to maintain hemodynamic homeostasis. Although anthracycline-induced heart failure is generally considered to be irreversible, some reports on complete recovery of cardiac dysfunction have been published (13).

The severity of anthracycline-induced cardiomyopathy can be quantified with the help of a morphologic grading system (14). In an endomyocardial biopsy, anthracycline toxicity is characterized by sarcotubular dilation and myofibrillar loss of actin and myosin. Long-term myocardial damage has also been identified in patients who had received doses of only 45 mg/m² (15). Therefore, all patients exposed to anthracyclines should be considered at risk for the development of heart failure as a result of the cardiotoxic properties of these agents. To evaluate cardiotoxicity, guidelines for monitoring cardiac function have been implemented in most anthracycline-containing chemotherapeutic regimens (16). The treatment of anthracycline-induced heart failure does not differ from the general pharmacotherapeutic approach to heart failure patients. Diuretics, angiotensin-converting enzyme inhibitors and digoxin are the mainstays of treatment. In some patients with severe anthracycline-induced CHF, heart transplantation may finally remain the only therapeutic option.

**Cyclophosphamide.** Cyclophosphamide is an alkylating agent that causes cytotoxicity by its biologically active metabolites. Reports have been published on both completely reversible cases as well as on fatal cases of CHF attributed to cyclophosphamide-induced cardiomyopathy (17,18). Cardiotoxicity of cyclophosphamide is thought to be due to toxic endothelial damage followed by extravasation of toxic metabolites with resultant myocyte damage and interstitial hemorrhage and edema (19). Symptoms of CHF usually appear within two weeks after administration of the drug. In patients who develop severe progressive CHF, this complication may lead to death within a few weeks. Based on analyses of the plasma concentration time curves (area under the curve, AUC) in 19 women with metastatic breast cancer, treated with a continuous 96-h infusion of cyclophosphamide, it has been shown that a low AUC and a low peak plasma level of cyclophosphamide were predictive for both an increased duration of response as well as for an increased risk of developing CHF. These findings suggest that patients with a more extensive metabolism of cyclophosphamide are more prone to develop cyclophosphamide-induced cardiotoxicity. In this way, measurement of the AUC may draw attention to those patients who are most susceptible
to develop heart failure. The numerous reports on both reversible and irreversible heart failure indicate a wide spectrum of cyclophosphamide-induced cardiotoxicity, which can be influenced by preexisting cardiovascular condition, other chemotherapeutic regimens received before treatment with cyclophosphamide and the dose and method of administration of cyclophosphamide (20).

**Paclitaxel.** Paclitaxel belongs to an important new class of anticancer agents, the taxanes. Paclitaxel promotes the polymerization of tubulin. Microtubules formed in the presence of paclitaxel are extraordinarily stable and dysfunctional. These dysfunctional microtubules interfere with normal cell division and interphase processes and may eventually lead to cellular death. Paclitaxel is increasingly used in the treatment of patients with advanced ovarian and breast cancer. Transient asymptomatic bradycardia appears to be the most frequent cardiovascular adverse effect, reported in up to 29% of the patients treated with paclitaxel (21). Clinically important cardiac bradyarrhythmias appear to have an incidence of only 0.1%. In a case report, the onset of heart failure has been associated with the administration of paclitaxel (22). Furthermore, heart failure has been reported with a remarkable frequency in an uncontrolled study of Gianni et al. in which women with metastatic breast cancer who had never received chemotherapy were treated with the combination of paclitaxel by 3-h infusion and doxorubicin (23). Six out of 33 patients (18%) developed symptomatic heart failure within 12 months after starting this treatment. The median received dose of doxorubicin in these patients was 480 mg/m². Based on previous studies, an incidence of symptomatic heart failure in the range of 1% to 10% should be expected within one year after treatment with doxorubicin at the commonly used total dose limit of 550 mg/m². Therefore, an incidence of 18% has raised the question whether the combined treatment of paclitaxel and doxorubicin may account for this apparently increased risk of heart failure. Other studies, however, in which different schedules of the combined administration of paclitaxel and doxorubicin were used did not indicate an increased risk of heart failure (23). This finding may suggest that the schedule used for the administration of paclitaxel and doxorubicin may influence the risk of CHF. On the other hand, as all patients who developed CHF in the study of Gianni et al. had cardiovascular risk factors or a history of mitoxantrone should be regarded as a potentially cardiotoxic agent that may be associated with drug-induced CHF.

**Other chemotherapeutic agents.** Heart failure has been associated with several other chemotherapeutic agents such as 5-fluouracil (5-FU) and cytarabine. Cardiac toxicity induced by 5-FU is usually characterized by chest pain and signs of ischemia, which resemble angina pectoris and is generally accepted to be caused by 5-FU–induced coronary spasms (26). There have also been reports in which the occurrence of severe but reversible left ventricular dysfunction was attributed to use of 5-FU (27–29), although the extent to which 5-FU may have accounted for the occurrence of CHF is not always obvious. As a result of 5-FU–induced coronary spasm, decreased ventricular function may also be caused by myocardial ischemia instead of by a direct toxic effect on the myocardium (30). In a retrospective study on cardiotoxic effects of 5-FU and folinic acid in 390 patients treated for gastrointestinal cancer, heart failure occurred in only one patient (31). Therefore, the association between heart failure and 5-FU should be evaluated in future studies. Cytarabine–induced reversible CHF seems to be very rare and has only been described in a case report (32).

Recently, Herceptin (recombinant humanized anti-HER2 antibody) has been approved for the treatment of breast cancer in the U.S. Herceptin inhibits the growth of cancer cells overexpressing HER2. The HER2 gene encodes a transmembrane tyrosine–kinase receptor, designated p185HER2. Antibodies directed at p185HER2 have been shown to inhibit growth of tumors that express high levels of this receptor (33). As overexpression of HER2 appears to be present in a considerable number of patients suffering from breast, ovarian and gastric cancer, Herceptin may be of value in the treatment of several different cancers. A recent study has shown that patients whose tumor cells have increased levels of p185HER2 do significantly better when Herceptin is added to standard chemotherapy. How-
ever, concern has been raised on cardiac toxicity, which occurred in a number of patients participating in a trial on breast cancer treatment. About 27% of the patients using doxorubicin, paclitaxel and Herceptin experienced signs of cardiac dysfunction, compared with 6% of those using only doxorubicin and paclitaxel (34). Although Herceptin may be considered as a potential improvement in the treatment of cancer, its cardiac toxicity might restrict its applicability in clinical practice. Therefore, cardiac toxicity should be a major point of concern in ongoing and future trials.

ANTIARRHYTHMICS

The cardiodepressant adverse effects of antiarrhythmic drugs can mainly be attributed to their negative inotropic properties. Particularly, in patients with preexistent left ventricular impairment, antiarrhythmics can induce or exacerbate CHF. Proarrhythmic effects that may occur during treatment with antiarrhythmics may further contribute to the induction or worsening of CHF. The degree of negative inotropy may vary from drug to drug. Class III antiarrhythmics, however, are usually considered as lacking these negative inotropic properties. Pathophysiologically, the negative inotropic effects of antiarrhythmic drugs are mediated by alterations of the intracellular calcium content (35). The ultimate effect on myocardial contractility of antiarrhythmics does not only depend on their true negative inotropic effect, but also on additional effects on the peripheral circulation, preexisting myocardial function and their effect on the prevailing arrhythmia.

Patients with decreased left ventricular function are at increased risk of both ventricular and supraventricular arrhythmias. Sudden death, attributed to the occurrence of an acute ventricular arrhythmia, is frequently encountered in patients with CHF. Not only are patients with impaired left ventricular function more prone to develop cardiac arrhythmias, but the cardiac arrhythmia itself may have a deleterious effect on left ventricular performance. Therefore, despite their potential negative inotropic effects and proarrhythmic effects, antiarrhythmic drugs are frequently needed in patients with CHF (36).

Randomized double-blinded placebo-controlled trials have indicated an increased risk of CHF for those patients assigned to treatment with an antiarrhythmic drug (37,38). Although most antiarrhythmic drugs have intrinsic negative inotropic effects and have been associated with the occurrence of CHF (39–45), there seem to be differences among the various antiarrhythmic agents (39–45). In a randomized crossover study in 21 patients with severe left ventricular impairment (mean left ventricular ejection fraction 21%), tocainide and encainide were significantly more likely to cause hemodynamic and clinical deterioration as compared with procainamide (46). Conclusions should be cautiously drawn, however, as the results may have been influenced by dose and route of administration of the antiarrhythmic drug and the evaluation of only the short-term effect of a single dose. Despite some differences among the various antiarrhythmic agents, nearly all antiarrhythmic drugs should be considered as potentially disadvantageous with respect to left ventricular contractility.

BETA-ADRENOCEPTOR ANTAGONISTS

Congestive heart failure is a well-known adverse effect of beta-adrenoceptor antagonists (beta-blockers). The negative chronotropic and negative inotropic properties of these drugs can easily induce or exacerbate CHF in patients with a propensity to this condition. Interestingly, also the topical administration of beta-blockers in patients with glaucoma has been associated with the occurrence of CHF in some case reports (47–49). Convincing evidence of systemic effects after topical administration of beta-blockers has been provided (50–54). In a pharmaco-epidemiologic study using automated databases, however, no relation between the use of topical beta-blockers and the occurrence of CHF could be revealed (55). Apart from methodologic limitations, this finding only indicates that on a population level, the topical administration of beta-blockers does not appear to be associated with a significantly increased risk of hospitalization for CHF. In susceptible individuals, however, the systemic effects of topical beta-blockers may suffice to induce or exacerbate CHF.

Interestingly, a new approach to the management of CHF includes the use of beta-adrenergic antagonists. As activation of the sympathetic nervous system is considered to be an important pathophysiologic mechanism in the progression of CHF, interference with the activated sympathetic nervous system appears to have beneficial effects in animal models of CHF (56,57). Although long-term trials on the effects of metoprolol and bisoprolol did not provide convincing evidence with respect to reduction of morbidity and mortality in patients with CHF (58,59), a recent trial with carvedilol demonstrated a reduced risk of death and hospitalization for cardiovascular causes (60). Carvedilol is one of the new beta-adrenergic agents with alpha-1–blocking and antioxidant properties. As a result of these additional properties of carvedilol, it remains unclear whether its favorable effects should be attributed to its beta-adrenergic antagonistic effect or to the additional properties of this agent. Ongoing additional studies on the effects of beta-adrenergic antagonists should demonstrate to what extent these drugs can contribute to the current treatment of patients with CHF. To prevent acute beta-adrenergic antagonistic effects in patients with CHF, starting dosages should be low and can be gradually increased if tolerated.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

Nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with fluid retention and the onset of CHF in several publications (61–66). Congestive heart failure which is induced or exacerbated by NSAIDs is not mediated by a
direct myocardial depressant effect of NSAIDs. The major mechanism of action of NSAIDs is the interference with prostaglandin (PG) biosynthesis by inhibiting the function of the enzyme cyclooxygenase (COX) (67). Furthermore, NSAIDs also interfere with the effects of diuretics and angiotensin-converting enzyme inhibitors (68–70). In healthy individuals, PGs play a negligible role in maintaining renal blood flow and consequently, NSAIDs usually exert no significant effects on renal hemodynamics (71,72). In patients with an impaired left ventricular function, however, PGs play an important role in the maintenance of cardiovascular and renal homeostasis. Prostaglandins have a vasodilatory effect on the afferent arteriole, oppose the effects of angiotensin II on the systemic circulation and decrease total body sodium and water. These effects of PGs are considered to contribute significantly to the maintenance of compensated heart failure in patients with impaired left ventricular function. In these patients, NSAIDs may interfere with cardiovascular homeostasis and may induce or exacerbate CHF (73).

Two isoforms of COX have been identified, COX-1 and COX-2. Cyclooxygenase-2 is predominantly involved in all stages of the inflammatory response, whereas COX-1 is mainly responsible for the synthesis of prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and PGI\textsubscript{2} in kidney and stomach (67). To prevent the potentially adverse effects on renal function, so-called renal-sparing NSAIDs have been introduced, such as sulindac, nabumetone and meloxicam. These agents have been reported to exert less adverse effects on renal function (74–78). However, comprehensive data on the effects of these agents on renal function and cardiovascular homeostasis in patients with decreased left ventricular function are not yet available.

**CALCIUM CHANNEL BLOCKING AGENTS**

For many years, there has been concern about the extent to which calcium channel blocking drugs may contribute to the exacerbation of CHF in patients with preexisting left ventricular dysfunction. As calcium channel blocking drugs are widely prescribed for the treatment of angina pectoris in patients with preexisting left ventricular impairment, this concern should be regarded as fully legitimated. Most calcium channel blockers currently approved for clinical use belong to three distinct chemical classes: the phenylalkylamines (e.g., verapamil), the dihydropyridines (e.g., nifedipine) and the benzothiazepines (e.g., diltiazem). In the SOLVD trial, calcium antagonists were found to be used in 30% of patients with CHF (79). Several pathophysiologic mechanisms that contribute to the potential effects of calcium channel blocking on left ventricular function have been described (80). These mechanisms can be characterized by a negative inotropic effect on the heart, caused by impeding the transmembrane cellular calcium transport, and the activation of endogenous neurohormonal systems such as the renin–angiotensin system and the sympathetic nervous system. Marked hemodynamic and clinical deterioration can occur in patients with CHF when the negative inotropic effects of calcium channel blockers are not counterbalanced by their vasodilatory effects (81,82). It has been postulated that the ability to improve the vascular compliance of the arterial tree may be a crucial determinant with respect to the effect of a particular calcium channel blocker on the natural course of CHF (83). This may also be an explanation for the observed effects of calcium channel blockers on the occurrence of CHF in some trials. In the Multicenter Diltiazem Postinfarction Trial (MDPIT), postinfarction patients with a baseline ejection fraction of less than 0.40 who were treated with diltiazem had a statistically significantly increased risk of subsequent CHF (84). The risk of CHF rose progressively with increasing impairment of left ventricular ejection fraction at baseline. Life table analysis excluded the possibility that the observed effect could be attributed to improved survival of those patients who were treated with diltiazem. However, some caution with respect to these findings is warranted, as the hypothesis was formulated after completion of the study. Furthermore, the diagnosis of CHF was not required to satisfy specific predefined criteria. Although the double-blind design of the study prevents any differential misclassification, a complex clinical syndrome such as CHF should preferably comply with well defined diagnostic criteria. Although calcium channel blockers intrinsically depress myocardial contractility, increased left ventricular ejection fraction can be observed after the administration of dihydropyridines such as nifedipine. This can be explained by the reflex stimulation of the sympathetic nervous system which counterbalances the intrinsic negative inotropic effect of the dihydropyridines (85). However, it has been shown that chronic administration of nifedipine in patients with CHF may have deleterious effects (86). Recently, results from the PRAISE-trial (Prospective Randomized Amlo- dipine Survival Evaluation Trial) indicated that amlo- dipine 5 to 10 mg/day in patients with CHF had no significant effect on cardiovascular events and mortality (87). Subgroup analyses in this trial pointed out that the benefit of amlo- dipine was only seen in patients with nonischemic cardio- myopathy. In a similar trial (V-HeFT III), felodipine showed neither beneficial nor unfavorable effects as compared with placebo (88). Although the vasodilatory effects of calcium channel blockers should be regarded as beneficial for patients with CHF, the negative inotropic effect and activation of neurohormonal systems by calcium channel blockers have unfavorable effects in these patients. Amlo- dipine, one of the newer dihydropyridines, may be of benefit in patients with nonischemic cardiomyopathy.

**ANESTHETICS**

During general anesthesia, cardiovascular homeostasis will be subject to several influences. Patient characteristics, such as age and concomitant comorbidity, intravenous fluid
administration, surgical procedures and medication used during general anesthesia may all affect cardiovascular homeostasis. Therefore, the occurrence or exacerbation of signs and symptoms of CHF in close relationship with general anesthesia cannot always easily be attributed to a specific agent used during general anesthesia. Nevertheless, a number of agents that are used during general anesthesia may have negative effects on myocardial contractility. The halogenated volatile anesthetics halothane and enfurane both have mild negative inotropic effects (89). In particular, halothane has been associated with cardiodepressant effects (90). Negative inotropic effects, however, have been found to be more pronounced in patients with preexisting left ventricular impairment (91). Cardiodepressant effects seem to be less frequent when using newer agents such as isoflurane and desflurane, although it has been suggested that these differences may apply only to young patients (92). The intravenous barbiturate anesthetics thiopental and methohexital may also depress myocardial contractility. In general, the hemodynamic consequences of usual plasma levels of these agents are limited (93). In patients who are more susceptible to the potential cardiodepressant effects of these agents, such as the elderly and patients with impaired left ventricular function, cautious dosages and proper fluid administration may prevent undesirable hemodynamic effects.

Propofol is an intravenous induction anesthetic that is also used for sedation in intensive care units. Most frequently reported adverse effects are bradycardia and hypotension. The hypotensive effect of propofol is considered to be brought about by peripheral vasodilation, inhibition of the sympathetic nervous system and reduced myocardial contractility (94). Long-term sedation with propofol in children has been associated with fatal myocardial failure, whereas the use in adults appears to be safe with respect to this effect (95). It has been suggested that the relatively high dosages might be responsible for the deleterious effects in children.

IMMUNOMODULATING DRUGS

Interferons. Three types of interferons, interferon-alpha, interferon-beta and interferon-gamma, are used for clinical indications. Interferon-alpha and -beta exert antiviral and antiproliferative activities, whereas interferon gamma acts primarily as an immunoregulatory cytokine. Interferon-alpha has been associated with cardiovascular adverse effects, such as hypertension and tachycardia during the first days of treatment in 5% to 15% of the patients (96). Cardiac adverse effects of the interferons are cardiac arrhythmias, cardiomyopathy and symptoms of ischemic heart disease (97). There have been case reports on both reversible and irreversible severe CHF after treatment with interferon-alpha (98–100). A clear pathophysiologic understanding of interferon-alpha-induced cardiomyopathy is lacking. Both impairment of myocyte metabolism as well as increased oxygen demand as a result of fever and tachycardia may be involved in the onset of CHF (98,100). Until now, interferon-beta has not been associated with the onset of CHF (97). Cardiovascular effects attributed to treatment with interferon-gamma, such as hypotension and arrhythmia, have been observed in patients treated with high dose interferon-gamma. In most instances, these patients had a history of preexistent cardiovascular disease. Although cardiovascular adverse effects seem to be infrequent, CHF has been reported as a possible adverse effect of interferon-gamma (102).

Interleukin-2. Interleukin-2 (IL-2), which has been approved for the treatment of metastatic renal cell carcinoma, may have serious cardiovascular adverse effects. Hypotension and tachycardia are almost invariably encountered in patients treated with IL-2. Reversible left ventricular dys-function has also been demonstrated in patients treated with IL-2, using echocardiography or radionuclide ventriculography (103,104). It has been suggested that the production of cytokines may have a central role in the development of IL-2–induced cardiac dysfunction. Cytokines may inhibit the accumulation of cellular cyclic adenosine monophosphate, which may blunt myocardial contractility. Histologic findings of eosinophilic and mixed lymphocytic–eosinophilic myocarditis attributed to IL-2 indicate a possible drug hypersensitivity syndrome (105).

ANTIDEPRESSANT DRUGS

Antidepressant drugs are usually divided into three main categories: classical antidepressants (mainly consisting of the tricyclic compounds), second generation antidepressants (including the selective serotonin reuptake inhibitors [SSRI]) and monoamine oxidase inhibitors. The cardiovascular effects of the tricyclic antidepressants (TCAs) have always been a source of concern, in particular when the prescription of a TCA is indicated in patients with cardiovascular comorbidity. Sinus tachycardia occurs in the majority of patients treated with TCAs, and approximately 20% of the patients may experience postural hypotension (106). Tricyclic antidepressant–induced postural hypotension is attributed to the combined effect of its peripheral antiadrenergic action, its myocardial depressant effect and its alpha-adrenergic blocking effect in the central nervous system. Compared with other TCAs, nortriptyline is only rarely associated with the occurrence of orthostatic hypotension (107). Tricyclic antidepressants also affect atrioventricular conduction by prolongation of the conduction time in the His bundle and the bundle branches, prolonging the duration of QRS interval and corrected QT interval (108). Second- and third-degree atrioventricular block may occur and lead to asystole and sudden death. Tricyclic antidepressants are highly concentrated in myocardial tissue, which partly explains their interference with heart rate, cardiac rhythm and myocardial contractility. The effects of TCAs on myocardial function are mediated by several mechanisms, such as their anticholinergic and quinidine-like
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action, interference with the reuptake of adrenergic amines, alterations of membrane permeability and direct myocardial depression (42). Several studies have been performed on the effects of TCAs on left ventricular function. There have been case reports of CHF attributed to the use of TCAs (109,110). Experiments in animals indicate that TCAs may have a negative inotropic effect (111), particularly in higher doses, although the findings from these experimental animal studies are difficult to extrapolate to human subjects. Results from noninvasive studies in which systolic time interval measurements are used as a parameter of left ventricular function suggest that TCAs impair cardiac function (112,113). However, the systolic time interval depends on cardiac conduction, which may have been influenced by TCAs. Therefore, these indirect measurements of left ventricular function do not provide convincing evidence of a direct TCA-induced cardiodepressive effect at the level of myocardial cells. More recent studies in which left ventricular contractility was assessed by radionuclide ventriculography failed to demonstrate TCA-induced left ventricular impairment. In 20 nondepressed patients with moderate to severe baseline ventricular impairment who were treated with imipramine (mean daily dose 210 mg) or nortriptyline (mean daily dose 100 mg) for ventricular premature depolarizations, no significant changes in mean ejection fraction could be observed (114). Studies of Veith et al. and Glassman et al. in patients with decreased baseline ejection fraction also indicate that TCAs have no significant effects on left ventricular ejection fraction (115,116). These studies, however, are characterized by a small sample size, selection of patients and a short period of follow-up. Despite these limitations, most studies indicate that the effects of TCAs on left ventricular function seem to have no major consequences for their applicability in everyday clinical practice. Even in patients with preexistent left ventricular impairment, there is no convincing evidence indicating that TCAs are likely to have deleterious effects on left ventricular function. However, as CHF is frequently accompanied by disturbances of cardiac conduction or low arterial blood pressure, and long-term information on the effect on ventricular performance of TCAs in heart failure patients is scarce, clinicians should be aware of possible adverse cardiovascular effects when prescribing TCA to patients with severe CHF.

Selective serotonin reuptake inhibitors have a very low rate of adverse cardiovascular effects. It has been estimated that the incidence of adverse cardiovascular events is under 0.0003% (117). This estimate, however, is based on reported cases of cardiovascular events to the pharmaceutical company. Although estimates of the incidence of adverse reactions that are based on the number of reported cases should be regarded with caution, the overall impression is that SSRI have a very low incidence of adverse cardiovascular effects. Probably the most important effect of SSRI in patients with cardiovascular comorbidity is their potential to interact with drugs that these patients are taking for cardiac arrhythmias, CHF or hypertension. The interaction between SSRI and several drugs is mediated by the inhibition of cytochrome P450 enzymes by the SSRI. The SSRI-induced inhibition of cytochrome P450 affects the metabolism of several classes of drugs, such as antiarrhythmics, beta-blockers, antihistamines and calcium channel blockers. It has been suggested that this might have been the cause of some unexpected deaths in patients who had recently begun fluoxetine therapy (118). As SSRI are a relatively new class of drugs, no studies have been performed on their effects on ventricular function in patients with CHF. Currently available data on the cardiac effects of SSRI suggest that these agents do not have direct influence on myocardial function, but that attention should be drawn to their potential interactions with several classes of drugs (117,119).

MISCELLANEOUS AGENTS

Apart from the categories of drugs discussed in the previous paragraphs, various other agents have been associated with the occurrence or worsening of CHF (see Table 1). Although the pathophysiologic mechanism is rather straightforward with respect to some agents, for example, mineralocorticoid effects of steroidal hormones, in other instances their causal role remains more obscure. In particular, when a pathophysiologic mechanism appears to be absent, the possibility of coincidence can hardly be ruled out. Nevertheless, detailed documentation of all clinical features of patients with suspected drug-induced CHF, even in the absence of a straightforward pathophysiologic explanation, may finally contribute to an objective risk–benefit profile of the agents involved.

CONCLUSIONS

Several categories of drugs may potentially induce or exacerbate CHF. Pathophysiologically, drugs that increase preload, afterload or have negative inotropic properties may be able to cause this adverse reaction. In Table 1, a distinction has been made between agents that are commonly regarded as being able to induce CHF in patients with previously normal ventricular function and agents which may precipitate CHF in patients with previously compensated CHF. Obviously, agents that may induce CHF can also precipitate CHF. Agents reported to induce CHF only very rarely are mentioned in this table as a third category. Particularly patients with preexisting left ventricular dysfunction who already have the propensity to develop CHF appear to be at risk for drug-induced heart failure. Although the cardiotoxic effects of drugs such as the anthracyclines and cyclophosphamide are obvious and well known, this is not always the case in all the categories of drugs we discussed. Moreover, drug-induced cardiac rhythm disorders may also induce signs and symptoms of CHF in susceptible patients. There-
Table 1. Drugs Associated With the Onset or Worsening of Congestive Heart Failure

<table>
<thead>
<tr>
<th>Agents associated with the induction of CHF</th>
<th>Agents associated with the precipitation of CHF in patients with preexisting ventricular dysfunction</th>
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<tbody>
<tr>
<td>Anthracyclines</td>
<td>Calcium channel blockers</td>
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<td>Paclitaxel</td>
<td>NSAIDs</td>
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<td>Mitoxantrone</td>
<td>Antiarhythmics</td>
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<td>Interferons</td>
<td>Beta-receptor antagonists</td>
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<td>Interleukin-2</td>
<td>Steroidal hormones with mineralocorticoid effects</td>
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<td>Drugs that may increase afterload:</td>
<td>NSAIDs</td>
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<td>Sympathomimetic drugs; e.g., adrenaline, dobutamine, dopamine</td>
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<td>Cyclosporine 120</td>
<td>Steroidal hormones with mineralocorticoid effects</td>
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<td>Agents that are only incidentally associated with the onset of CHF in case reports</td>
<td>Steroidal hormones with mineralocorticoid effects</td>
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<td>Aminocaproic acid (123)</td>
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<td>Antidigoxine antibody fragments (124)</td>
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<td>Sodium-containing antacids (42)</td>
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<td>Amantadine (125)</td>
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<td>Bromocriptine (42)</td>
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<td>Foscarnet (126)</td>
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<td>Mannitol (128)</td>
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<td>Hydralazine (42)</td>
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<td>Edetic acid (42)</td>
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<td>Difenprone (129)</td>
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<td>Dapsone (130)</td>
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<td>Carbamazepine (42)</td>
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<td>Cibenzoline (131)</td>
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<td>Prostaglandin E2 (132)</td>
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<td>Methyl-sergide (42)</td>
<td>Steroidal hormones with mineralocorticoid effects</td>
</tr>
<tr>
<td>Ilosfamide (133)</td>
<td>Steroidal hormones with mineralocorticoid effects</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; NSAID = nonsteroidal anti-inflammatory drug.

Therefore, detailed documentation of the medication involved together with all clinical features of patients with suspected drug-induced CHF may contribute substantially to a reliable assessment of both the pathophysiologic mechanism and the likelihood of causality. This may finally serve as an appropriate risk–benefit profile of the drugs involved.

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