C. Role of Digitalis

There is some controversy regarding the efficacy of digitalis glycosides in chronic heart failure. However, patients with cardiac dilatation may be successfully treated as noted previously. Opinions differ regarding the indications for digitalization. The question is whether, in an individual case, the positive effects of digitalis therapy outweigh the potential side effects. Even more difficult to answer is the question whether a specific patient actually requires digitalis treatment. Proper dose selection is particularly important because of the low therapeutic margin of safety. If a patient is already on digitalis, continuous monitoring is necessary to decide if the maintenance dose is appropriate, for detection of side effects, and accurate determination of serum concentrations (Eliot et al. 1980).

A specific indication for digitalis is chronic heart failure. The usual prerequisite is an enlarged heart usually associated with substantial left or right ventricular injury. The electrophysiologic inhibitory effects on the atrio-ventricular node are significant and may be particularly useful in patients with atrial fibrillation. Atrial fibrillation and congestive heart failure are the major indications for the use of digitalis glycosides.

I. Mechanism of Action of Digitalis Glycosides

1. Molecular Mechanism

The molecular mechanism of action of digitalis has largely been elucidated on the cellular level (see review by Erdmann 1982). The effects of digitalis are explained on the basis of its influence on intracellular sodium and potassium concentrations. Cardiac glycosides exert a selective and reversible inhibitory action on sodium-potassium ATPase and consequently, on the active \( \text{Na}^+ / \text{K}^+ \) transport across the cell membrane. This is the reason why the sodium-potassium ATPase has also been called the “digitalis receptor” (Repke and Portius 1963). A distinct increase in intracellular calcium concentration occurs but it has not been determined if this is due to the glycoside-related intracellular accumulation of sodium. The elevated intracellular calcium concentration then leads to an enhanced activation of contractile proteins via increased binding to troponin.

This model of glycoside activity consisting of receptor, sodium-potassium ATPase, \( \text{Na}^+ - \text{K}^+ \) exchange, contractile proteins provides the explanation for numerous clinical interactions. Potassium reduces the receptor affinity for cardiac glycosides. This explains the increased incidence of digitalis toxicity observed with hypokalemia. On the other hand, therapeutic administration of potassium is recommended for a moderate digitalis overdose or for cardiac arrhythmias.
pokalemia as well as hyperthyroidism are associated with an increase in the number of cardiac glycoside receptors. With severe digitalis intoxication, the marked inhibition of sodium-potassium ATPase results in large potassium losses from the cell with a subsequent elevation of the serum potassium level.

2. Hemodynamic Effects

In the presence of heart failure, the positive inotropic effect of digitalis glycosides leads to an increase in stroke volume and cardiac output and a moderate reduction of right and left ventricular filling pressures. In the absence of heart failure, this positive inotropic effect may be seen by noting an increase in left ventricular contractility but not an increase of stroke volume (Bussmann et al. 1969). Without the presence of heart failure, digitalis glycosides produce mild vasoconstriction in the venous and arterial beds.

II. Contraindications

A clear contraindication for digitalis treatment is a second- or third-degree AV block and in some cases, a first-degree AV block as well. Patients with hypertrophic obstructive cardiomyopathy are also excluded from digitalis treatment because the inotropic effect increases the obstruction to outflow.

At the present time, relative contraindication to digitalis use is acute heart failure. This primarily should be treated with vasodilating agents, occasionally supplemented with diuretics.

The previously stated opinion that acute myocardial infarction was a classic indication for cardiac glycosides is no longer valid (Blumenberger 1963). The post-infarction phase, unless associated with a substantial ventricular dysfunction resulting in cardiomegaly, presents no clear indication for digitalis use. The study by Moss et al. (1981) demonstrated that early mortality of postinfarction patients is five times higher with the use of digitalis than without. These findings were met with opposition. However, digitalization in the post-infarction state must be critically evaluated.

Typical digitalis therapy as it was formerly used in older patients has been abandoned. It was previously thought that digitalis was "the milk of old age". On the contrary, particularly in older patients, indications for the use of digitalis must be carefully considered. A clearly enlarged heart is a valid guideline. Since in the older patient creatinine clearance is reduced (mean value 36 ml/min), the dose of digoxin must be reduced by 30 to 50 percent. Therefore, digitoxin preparations are preferable in the older patient.