Long-Term Use of K-Strophanthin in Advanced Congestive Heart Failure Due to Dilated Cardiomyopathy: A Double-Blind Crossover Evaluation Versus Digoxin

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Summary: K-strophanthin or digoxin were added to diuretics (all cases) and vasodilators (most cases) for treating advanced congestive heart failure in 22 patients with dilated cardiomyopathy and sinus rhythm. K-strophanthin (0.125 mg intravenously) or digoxin (0.25 mg orally) were administered daily in two 3-month periods, during which vasodilators and diuretics were kept constant and patients received one of the two digitalis preparations in a double-blind fashion, crossing over to the alternative preparation in the next period. Blindness was assured throughout the trial with a daily intravenous injection of 10 ml normal saline solution either containing K-strophanthin or not, and with daily oral administration of either placebo or active digoxin. At the end of the run-in period, 15 days after starting active preparations, and thereafter every month for the next 6 months, we evaluated left ventricular pump function at rest and patients' functional performance by a cardiopulmonary exercise test. At Day 15, cardiac index and ejection fraction at rest, compared with run-in, were significantly raised with both glycosides; during exercise while on K-strophanthin, peak oxygen consumption was augmented by 1.4 ml/min/kg ($p < 0.01$) and oxygen consumption at anaerobic threshold by 2.2 ml/min/kg ($p < 0.01$); corresponding variations on digoxin (-0.1 and $+0.3$, respectively) were not significant versus run-in. These patterns were duplicated at repeated tests during follow-up. In the entire population, means for oxygen consumption at peak exercise and at anaerobic threshold were raised from run-in values by 1.4 ($p < 0.01$) and 2.2 ml/min/kg ($p < 0.01$), respectively, after 3 months of K-strophanthin treatment, and by 0.0

and 0.1 ml/min/kg, respectively, after treatment with digoxin for the same period of time. Results were similar in nine patients when they were given digoxin intravenously (0.25 mg/day) for 1 week after having completed the trial with the oral digoxin preparation. These results indicate that K-strophanthin improved functional performance in patients with severe cardiac decompensation due to dilated cardiomyopathy; digoxin failed to provide the same results, independent of the drug sequence or the route of administration. The reasons for these differences are basically unknown and do not seem to be related only to changes in cardiac performance at rest, because both K-strophanthin and digoxin significantly and persistently raised cardiac output and ejection fraction at rest.

Introduction

In congestive heart failure, long-term treatment based on inotropic stimulation of the heart shows poor results.[1] Even though digoxin is, in most cases, the background of the antifailure therapy,[2–6] the efficacy of cardiac glycosides has been repeatedly questioned.[7, 8] K-strophanthin is a mixture of cardiac glycosides from strophanthus, which possesses the general properties of digoxin and has been used similarly.[9] It is poorly absorbed from the gastro-intestinal tract, but acts in 5–15 min after intravenous injection.[9] Because in patients with normal renal function its half-life is > 50% less than that of digoxin[9] and because of the necessity of an intravenous route, K-strophanthin has almost been neglected as a long-term remedy for the failing heart.

In a number of patients with dilated cardiomyopathy, in whom we utilized K-strophanthin as an emergency treatment for pulmonary edema and continued it for several days after its resolution, clinical improvement was impressive and persistent. Because congestive cardiomyopathy still is one of the most difficult and challenging therapeutic tasks in clinical cardiology, we felt that a potentially effective treatment should not remain unexplored. Thus, we performed a clinical study in which K-

strophanthin was tested in the long term and compared with digoxin in patients with advanced congestive heart failure due to dilated cardiomyopathy. Considering the severity of the clinical condition of these patients and, according to the study design, the necessity of repeated tests, we decided not to use invasive methods of investigation. Our study was based on assessment of the cardiac pump function at rest and on cardiopulmonary exercise testing, which is of recognized clinical value in measuring exercise tolerance, functional capacity, heart failure, and its response to treatment.[10, 11]

Methods

Population

Twenty-two patients in stable clinical condition and with overt congestive heart failure due to dilated cardiomyopathy (classes III and IV according to the New York Heart Association classification) were considered to be eligible. Two of these patients died, 1 was lost to follow-up, and 19 participated throughout the study. Treatment regimen before recruitment did not include digitalis or other inotropic agents for at least 1 month. No patient had atrial fibrillation, anginal symptoms, pulmonary, hepatic, valvular, or congenital cardiac diseases, or significant renal impairment. Criteria of inclusion involved recording of good-quality echocardiograms. Patients were deemed to be eligible for the study if they were capable of exercising for at least 3 min.

The study protocol was approved by the Ethical Research Committee of the Institute of Cardiology, University of Milan, and each patient gave written informed consent.

Study Design

Patients were admitted to the hospital and, during the first 7 days, blood and urine laboratory tests were performed and the dosages of diuretics and vasodilators were adjusted until an optimal regimen had been achieved (Table I). This regimen was kept constant during the trial. Patients were also familiarized with the laboratories and were exercised at least once.[11] The subsequent study design (Fig. 1) included (1) a run-in period of 10 days during which patients were given placebos of the two test drugs; (2) random allocation to a treatment group and beginning of a double-blind crossover follow-up (blindness was warranted by the daily intravenous injection of 10 ml normal saline solution either containing K-strophanthin or not, and daily oral administration of placebo or active digoxin); (3) discharge from the hospital within the next 15 days, with patients attending the outpatient clinic daily and receiving the test drug and placebo of the alternative drug for 3 months; (4) switch to the alternative test drug and continuation for the next 3 months. We considered a wash-out period to be unnecessary in view of the long treatment duration. Oral digoxin was given at a daily dose of 0.25 mg, which produced a serum level of 1.9–2.5 ng/ml. The daily intravenous dose of K-strophanthin was 0.125 mg (Kombetin, Boehringer Mannheim). At the end of the run-in period, 15 days after

TABLE I   Clinical data in 22 patients with congestive heart failure

Patient No.	Age	Gender	NYHA	Drug treatment
1	62	M	IV	Furosemide, spironolactone
2	38	M	III	Furosemide, captopril
3	74	M	IV	Furosemide, enalapril, spironolactone
4	71	F	III	Furosemide, spironolactone
5	64	M	III	Furosemide, nitrates
6	67	M	IV	Furosemide
7[a]	74	M	III	Furosemide, spironolactone, theophylline, nitrates
8	52	M	III	Furosemide
9	62	F	III	Furosemide, spironolactone, nifedipine
10	69	M	IV	Furosemide, spironolactone, captopril
11[b]	47	M	III	Amiloride
12	61	F	III	Furosemide
13	65	M	III	Furosemide, enalapril, spironolactone
14[a]	65	M	IV	Furosemide, nitrates
15	38	F	IV	Furosemide, enalapril
16	61	M	IV	Furosemide, captopril, spironolactone
17	62	M	IV	Furosemide, captopril, amiodarone
18	49	M	IV	Furosemide, captopril, spironolactone
19	56	M	IV	Furosemide, enalapril, spironolactone, ethacrinic acid
20	72	M	III	Furosemide, spironolactone, theophylline
21	39	M	III	Furosemide, captopril
22	63	M	IV	Furosemide, spironolactone

[a] Patient died, [b] patient lost to follow-up.
Abbreviations: M = male, F = female, NYHA = New York Heart Association functional class.
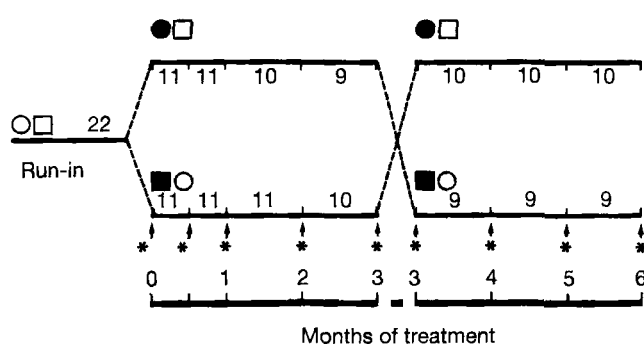

FIG. 1   Study protocol: The design of the study was cross-over and double-blind. Open and full symbols indicate placebo and active compounds of digoxin (square) and K-strophanthin (circle), respectively; numbers are patients participating in each step of the trial. * = Cardiopulmonary exercise test, cardiac output, left ventricular dimensions, digoxin, electrolytes, creatinine, and norepinephrine determinations.

treatments were started, and thereafter monthly for the next 6 months, 10 h after dosing, blood samples were drawn (after prolonged recumbency and 30 min after insertion of a catheter needle into an antecubital vein) for determination of creatinine, electrolytes, digoxin, and norepinephrine—the latter by high-performance liquid chromatography.[12] Thereafter, cardiac output and ultrasound left ventricular measurements were taken at rest and 2 h later patients underwent cardiopulmonary exercise testing. The nine patients who completed the trial on oral digoxin were switched to intravenous digoxin (0.25 mg a day administered with the same modalities as K-strophanthin) for 1 week, at the end of which the humoral, hemodynamic, and cardiopulmonary tests were repeated.

Ultrasounds

Records were obtained with the patient resting for 15 min in a comfortable semiorthostatic position, and included simultaneous measurements of left ventricular dimensions by two-dimensional echocardiography (Hewlett-Packard 77020/A, Andover, Mass.), cardiac output by the CO_2 rebreathing method (equilibrium technique, Sensor Medics MMC 4400, Anaheim, Calif.),[13] and blood pressure through sphygmomanometry. Ejection fraction was calculated from end-diastolic and end-systolic left ventricular diameters (mean of three consecutive beats) using the Teichholz formula.[14]

Cardiopulmonary Exercise Test

Cardiopulmonary exercise tests were performed on a cyclo-ergometer (Collins Pedalmate, Braintree, Mass.) 12 h after administration of the test compounds. The exercise protocol was as follows: 60 s of unloaded pedaling, 180 s of pedaling with a load of 10 W, followed by 10-W increments every 180 s. Exhaled gases were collected on a breath-by-breath basis (Sensor Medics MMC 4400, Anaheim, Calif.). Results of the tests in each patient were analyzed together in the same session by three independent experts who were blinded to the study protocol. Anaerobic threshold was determined by VCO_2/VO_2 analysis (V slope).[15] Oxygen consumption at anaerobic threshold and peak oxygen consumption are expressed as the oxygen consumption (ml/min/kg) in the 30 s in which anaerobic threshold and peak oxygen consumption, respectively, occurred.

Statistical Analysis

Data are reported as mean ± standard error. The effect of K-strophanthin versus digoxin and of K-strophanthin and digoxin versus placebo on the examined variables were analyzed by analysis of variance and Student's paired t-test, utilizing the Bonferroni correction when multiple comparisons were made.[16]

Results

Nineteen patients participated in the study and received active digoxin + intravenous saline solution or intravenous saline

containing K-strophanthin + placebo digoxin, for 3 months each in a double-blind crossover trial (Fig. 1). Both drugs reduced heart rate and raised cardiac and stroke indices and the ejection fraction of the left ventricle at rest (Fig. 2). Cardiac and stroke indices increased more with K-strophanthin. Associated with these changes there was a decrease of systemic vascular resistance and norepinephrine plasma concentration; differences from the run-in period, however, were statistically significant only when K-strophanthin was given. Mean exercise tolerance times (Fig. 2) on K-strophanthin were significantly better than baseline values or values on digoxin.

Figure 3 shows means for the same variables as reported in Figure 2 that were recorded in the entire population at the end of the run-in period and after the 3-month treatment with either agent. Changes induced by digoxin and K-strophanthin moved in the same directions as shown in Figure 2. This indicates that the sequence of the drug administration did not interfere with the quality of response to treatment.

As shown in Figure 4, oxygen consumption on K-strophanthin at peak exercise and at the anaerobic threshold both were
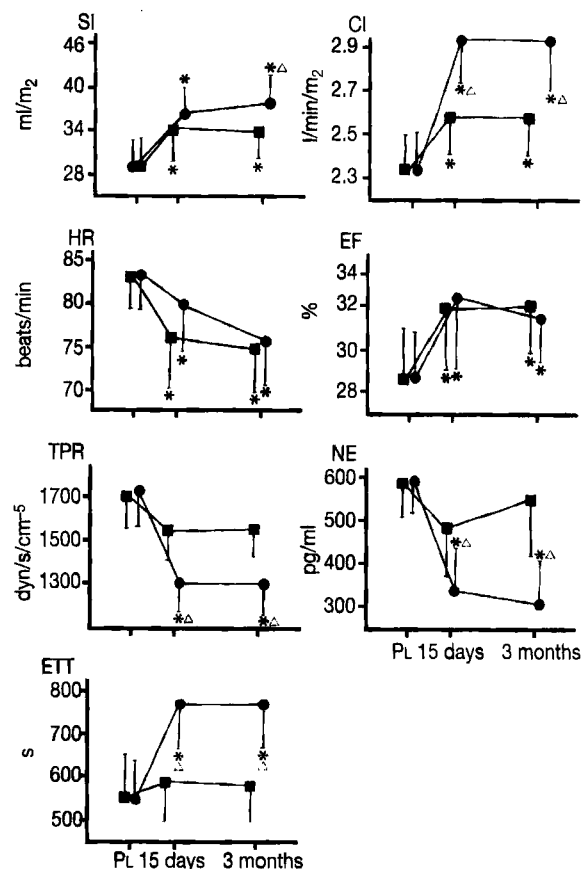

Fig. 2   Stroke index (SI), cardiac index (CI), heart rate (HR), ejection fraction (EF), total peripheral resistance (TPR), plasma norepinephrine (NE), and exercise tolerance time (ETT) in the first 3 months of the study with placebo (Pl) and active compounds (square = digoxin, circle = K-strophanthin). * = p < 0.01 versus placebo, = p < 0.01 versus digoxin.
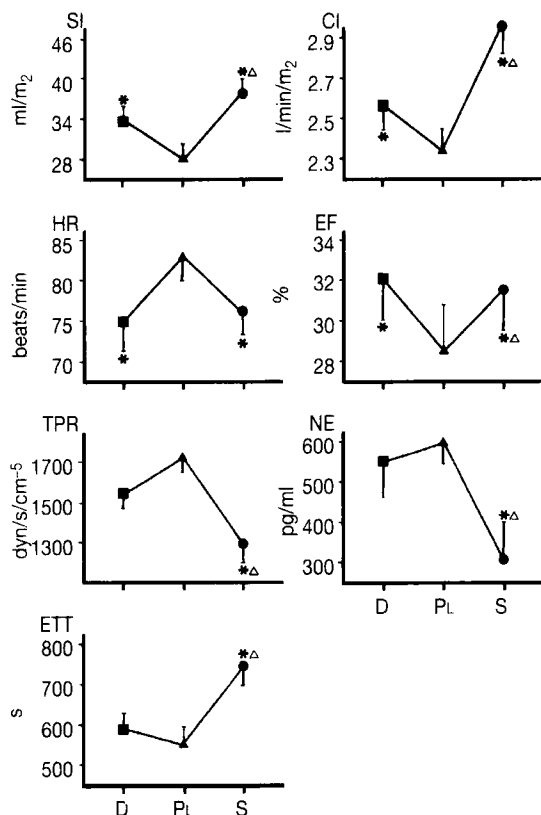
FIG. 3   Hemodynamic, exercise tolerance, and norepinephrine values (means ± SEM) of the entire population while on placebo (end of the run-in period) and after 3-month treatment with digoxin (D) and K- strophanthin (S). Abbreviations and symbols as in Figure 2.

FIG. 4   Comparison of oxygen consumption (ml/min/kg) at peak exercise (VO2p) and at anaerobic threshold (VO2at) during digoxin and K-strophanthin treatment. Open symbols indicate placebo (Pl) and were obtained at the end of the run-in period; full symbols indicate active compounds (square = digoxin, circle = K-strophanthin). * = p < 0.01 versus placebo, Δ = p < 0.01 versus digoxin. ■—■ = Digoxin, ●- - ● = K-strophanthin.

significantly higher than baseline values or values on digoxin. Digoxin treatment values were never significantly different from those in the run-in period. In Table II, exercise tolerance time, oxygen consumption at peak exercise and at anaerobic threshold, cardiac and stroke indices, ejection fraction, heart rate, systemic vascular resistance, and plasma norepinephrine recorded in nine patients after completion of the trial on oral digoxin are compared with those detected after the shift to intravenous digoxin for a week. Values were comparable in the two conditions.

No patients had to stop taking cardiac glycosides during the study because of adverse reactions; the reported dosages were well tolerated and accepted. No changes in renal function tests and serum electrolytes were recorded during active treatments. While on digoxin, digoxin plasma concentration ranged between 1.9 and 2.5 ng/ml.

Discussion

With muscle work, minute ventilation and oxygen consumption and delivery must each rise proportionately at a rate commensurate with the level of oxygen uptake to sustain aerobic skeletal muscle metabolism. With strenuous work, the ex-
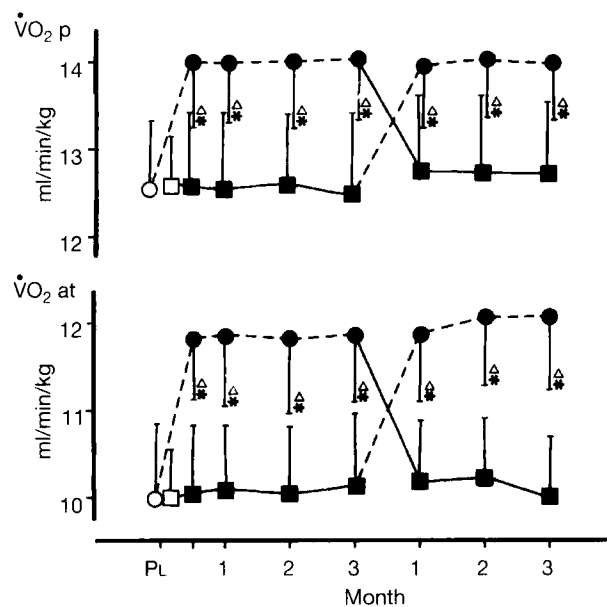
tent to which cardiac output and minute ventilation rise poses a limitation to the performance of aerobic work. Enhanced oxygen extraction and muscle vasodilatation are additional mechanisms to ensure oxygen availability to working muscles and to dictate the aerobic capacity. Beyond these limits, which reflect the maximal oxygen uptake, any additional increment in work is not accompanied by an elevation of oxygen utilization. The

TABLE II   Hemodynamic values, plasma norepinephrine, and results of cardiopulmonary tests in nine patients on oral digoxin and intravenous digoxin

	Digoxin	
	Oral	IV
Stroke index (ml/m²)	33.6 ± 3.1	33.1 ± 3.5
Cardiac index (ml/min/m²)	2590 ± 189	2612 ± 213
Heart rate (beats/min)	76 ± 6	78 ± 9
Ejection fraction (%)	30 ± 1.9	31 ± 2.4
TPR (dynes/s/cm⁻⁵)	1590 ± 186	1720 ± 197
Norepinephrine (pg/ml)	561 ± 134	542 ± 122
Exercise tolerance time (s)	580 ± 91	592 ± 88
VO2p (ml/min/kg)	12.7 ± 1.0	12.8 ± 1.1
VO2at (ml/min/kg)	10.1 ± 0.8	10.1 ± 1.0

Abbreviations: TPR = total peripheral resistance, VO2p = peak oxygen consumption, VO2at = oxygen consumption at anaerobic threshold.

maximal oxygen uptake, therefore, not only reflects aerobic capacity, but also the physiologic capacity of the cardiovascular system to deliver oxygen.[17] Anaerobiosis normally occurs when ≥ 60% of the subject's aerobic capacity has been attained. In patients whose cardiac output response is limited, lower work loads are required before working muscle becomes anaerobic and the anaerobic threshold is reached. Given that oxygen extraction by muscles is not impaired, the reduction in aerobic capacity of the patient with chronic cardiac failure will be primarily due to the heart's inability to sustain blood flow or to the muscle's inability to vasodilate.

The most direct manner in which an inotropic drug may raise the oxygen uptake and the anaerobic threshold is that of improving the performance of the heart and raising the limit of cardiac output response to exercise. Each of the two cardiac steroids used in this study significantly and persistently augmented cardiac output and ejection fraction at rest. However, exercise tolerance time and oxygen uptake at peak exercise and at anaerobic threshold all indicated that K-strophanthin, but not digoxin, improved the functional capacity of patients with severe cardiac decompensation. Failure of digoxin to provide this result is in agreement with the observations made by Fleg et al.[18] on ambulatory patients with mild to moderate congestive heart failure: despite improvement in left ventricular performance with digoxin during exercise, these authors were not able to record an enhancement of aerobic capacity. For the reasons mentioned in "Introduction," we utilized only noninvasive methods, and cardiac hemodynamics during exercise were not explored. As far as can be judged from findings at rest, the discrepancy between the two glycosides is not explained by left ventricular performance alone, unless it is admitted that, when the heart is failing, a threshold level of cardiac performance should be obtained to improve the patient's functional capacity and also that, of the two preparations, only K-strophanthin is able to do that in spite of its shorter half-life. The disparity is poorly understood but may have several speculative explanations. The intermittent inotropic stimulation may be more beneficial than a continuous one, and improvement may be relatively sustained as was proved for other inotropic drugs.[19] Cardiac output may be raised more following each K-strophanthin injection and adjustments to improved blood flow may occur in the peripheral vessels, skeletal muscles, kidneys, and myocardium. Endothelial relaxing factors may be stimulated by temporarily increased flow[20] and vasodilating capacity may be enhanced. Fibers of the failing heart may be overloaded with calcium; low concentrations of cardiac steroids may stimulate the sodium pump activity and may lower intracellular calcium to levels at which overload is reduced or eliminated and the force of contraction actually is increased.[21]

As shown in Figures 2 and 3, in the untreated condition these patients had an almost threefold rise from normal of circulating norepinephrine,[22] which was not affected by digoxin and was reduced by almost 50% by strophanthin. In heart failure, increase of plasma norepinephrine concentration goes parallel with the severity of the syndrome.[22] The elevated circulating levels generally are interpreted as reflecting sympathetic overactivity and overflow of the transmitter to blood.[23] Reduction of circulating

norepinephrine with inotropic therapy reasonably results from a positive interplay of several factors, among which improved blood flow, that attenuates the compensatory sympathetic drive, and resolution of congestion of organs like kidneys and lungs, where most norepinephrine is cleared,[24] may have an important part. Although the reasons for the discrepancy between the two cardiac steroids are once again elusive, it is tempting to suggest that reduction of the sympathetic transmitter facilitates vasodilatation and perfusion at the level of the exercising muscles and contributes to the improvement of functional performance with K-strophanthin.[25] A diminished activity of the adrenergic system is an additional explanation for the persistence of the beneficial effects on physical performance for longer than predicted from the kinetics of the drug: the augmented performance of the heart at rest detected several hours after dosing with K-strophanthin might, at least in part, be due to the reduced impedance to left ventricular ejection.

A therapeutic digoxin level was achieved in all patients and was, in some cases, even higher than is standard in clinical practice.[26] It is not established whether maximal tolerated doses might have promoted the same degree of physical performance as K-strophanthin did in this study. The evidence was convincing that the route (oral or intravenous) of administration of digoxin made no difference regarding cardiac hemodynamics at rest, circulating norepinephrine, and functional capacity. These considerations apply to patients with sinus rhythm and might not be appropriate in the presence of atrial fibrillation. In applying the results of this work, the clinician should note that when glycosides are used at current therapeutic dosages in patients with severe congestive heart failure and sinus rhythm, the influence on physical performance may vary from one preparation to another; cardiac function at rest and functional capacity may not vary in parallel; the pharmacokinetics may not be predictors of the drugs' clinical efficacy.

Conclusion

K-strophanthin may be viewed as an effective alternative for patients with advanced heart failure refractory to other cardiac steroids, provided this finding is confirmed by others. Inconveniences that derive from the intravenous route of administration and that may challenge the patients' compliance should be balanced against the severity of the prognosis; levels of circulating norepinephrine[22] and oxygen consumption at peak exercise[27] may assist in making an appropriate choice.

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