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Digoxin Use in Congestive Heart Failure

Current Status

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Contents

Summary

The use of digitalis in congestive heart failure with normal sinus rhythm is still debated. While older uncontrolled, withdrawal studies from 1969 to 1983 provided incomplete data, with poorly documented clinical status and poor haemodynamic and exercise data, some patients did improve clinically when digitalis treatment was utilised.

Randomised, double-blind, placebo-controlled trials from 1977 to 1991 were of better quality but still short in duration, with small sample sizes and still with incomplete haemodynamic and exercise data. In 1993, the Prospective Randomised Study of Ventricular Failure and Efficacy of Digoxin (PROVED) and Randomised Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) study, followed in 1997 by the Digitalis Investigation Group (DIG) trial, documented that digoxin prevents clinical deterioration and hospitalisations, and improves exercise tolerance and left ventricular function, but has no effect on survival.

A substudy of the DIG trial showed no detrimental effect of digoxin on survival in patients with ejection fraction (EF) of >45%, i.e. left ventricular (LV) diastolic dysfunction. Therefore, digoxin appears to be the first inotrope with no detrimental effect on survival in heart failure. In addition, the neurohormonal effect of digoxin has been documented, and is possibly present with dosages even lower than 0.25mg. Finally, it has been determined that patients with only mild heart failure do obtain documented benefit from administration of this drug.

Ever since the introduction of digitalis by William Withering in 1785,[1] physicians have been debating its value in congestive heart failure with normal sinus rhythm. Such a debate was that between two eminent clinicians, Sir James MacKenzie and Henry Christian, co-editors of *Oxford Medicine*, in 1922.[2] Sir James advocated the use of digitalis only in heart failure with associated atrial arrhythmias. Dr Christian argued that its effectiveness appeared to be irrespective of whether or not the pulse was irregular. Dr Arthur Hollman, biographer of Sir Thomas Lewis, was interviewed on American College of Cardiology ACCEL tape in June 1997 and said that Sir Thomas 'did not believe digitalis was a stimulant in heart failure with normal sinus rhythm'.[3] In this interview Dr Hollman's interpretation was that 'since the debate has continued for so long, digitalis must not be very valuable'.

Poole-Wilson and Robinson[4] considered digoxin a redundant drug in congestive heart failure in 1989, essentially superseded by angiotensin converting enzyme (ACE) inhibitors. After their review of 14 uncontrolled and 6 controlled clinical trials, they concluded that: (a) digoxin exerts a small, long term positive inotropic effect; (b) if no other drugs were available, digoxin would still be used but only in the more severe cases, not in mild heart failure; (c) risks exceed advantages, especially *post* myocardial infarction. As late as 1995, Dr Karl Weber reflected in a review article: 'I personally do not use digoxin for heart failure, except when there is associated atrial fibrillation'.[5]

No one argues over the effectiveness of digitalis in slowing atrioventricular (AV) conduction and the ventricular rate with atrial fibrillation, especially at rest. The purpose of this review is to discuss the current status of digitalis in heart failure with normal sinus rhythm.

1. Older Uncontrolled Withdrawal Trials, 1969-1983

The best reviews of these early trials are by Gheorghiade and Zarowitz,[6] Tauke et al.[7] and Gheorghiade.[8] The conclusion that can be reached is that some patients respond clinically and some do not, but objective data are few and incomplete. For example, the earliest study by Starr and Luchi[9] showed that when digitoxin was withdrawn from 11 women aged 73 to 94 years, some without heart disease, no clinical deterioration was observed. Dall[10] studied 80 patients, aged 58 to 99 years, some with atrial fibrillation and no heart disease, and no symptomatic deterioration was observed in approximately 75% of the patients with digoxin discontinuation.

The number of patients in these early trials ranged from 6 to 80, with 10 trials having 24 patients or less.[9-22] Three trials had patients with atrial fibrillation mixed in with individuals in sinus rhythm; duration of follow-up was less than 4 months in all cases, and only 2 trials determined ejection fraction.[9-13] Our conclusions are that: (a) no attempt was made to differentiate systolic versus diastolic left ventricular (LV) dysfunction; (b) there are incomplete data for heart failure in many, i.e. lack of documentation of symptoms and signs of heart failure; (c) there are no serial haemodynamic or exercise data; (d) there is wide variation in study design; and (e) therefore, we are left with the impression that digoxin may or may not help patients with heart failure with normal sinus rhythm. The data are simply too incomplete.

2. Randomised, Double-Blind, Placebo-Controlled Trials, 1977-1991

Gheorghiade and Zarowitz[6] and Yusuf et al.[23] reviewed 10 trials without a direct comparison of digoxin with an ACE inhibitor (table I). The difficulties in interpreting the data are exemplified by the trial by Dobbs et al.[24] in which 46 patients were studied, 13 of whom had atrial fibrillation. In a trial by Fleg et al.[25] only 1 of 30 patients was described as having a third heart sound gallop. No change in clinical status and/or exercise duration occurred with withdrawal of digoxin in a crossover study design.

Lee et al.[26] described 25 patients, but 10 of these (40%) had a heart failure score of 0 at baseline; 6 had an ejection fraction (EF) of >50%, and

Table I. Randomised, double-blind, placebo controlled trials (no ACEI) of digoxin in heart failure

Reference	Year	No. of pts	Duration (wk)	NYHA class	Clinical benefit	Comment
Dobbs et al.[24]	1977	46	6	NA	Yes	Included pts in atrial fibrillation; clinical improvement occurred with digoxin, clinical worsening associated with placebo
Fleg et al.[25]	1982	30	12	II/III	No	No clinical improvement but LVED dimension decreased with digoxin
Lee et al.[26]	1982	25	9	II/III	Yes	Clinical improvement and decrease in heart size with digoxin
Taggart et al.[27]	1983	22	12	I/III	No	No clinical improvement but systolic time interval improved with digoxin
Guyatt et al.[28]	1988	20	7	II/III	Yes	Improved symptoms, cardiothoracic ratio, fractional shortening and exercise capacity with digoxin
Captopril-Digoxin Multicenter Research Group[29]	1988	196	24	II/III	Yes	Improvement in EF, clinical status and exercise capacity
German and Austrian Xamoterol study Group[30]	1988	433	12	I/III	Yes	Symptomatic improvement
Dibianco et al.[31]	1989	230	12	II/III	Yes	Clinical improvement with increase in EF and exercise duration
Pugh et al.[32]	1989	44	8	NA	Yes	Increase in exercise capacity
Fleg et al.[33]	1991	12	4	II/III	No	Increase in EF with exercise but no impact on resting EF or exercise duration

Abbreviations: ACEI = angiotension-converting enzyme inhibitor; EF = ejaction fraction; LVED = left ventricular end diastolic; NA = not available; NYHA = New York Heart Association.

4 had hypertrophic cardiomyopathy. However, in the group of 19 patients with an EF of <43%, 14 improved with digoxin. Potentially the greatest benefit of this article was in identifying a subset of patients with a better response: a higher heart failure score, presence of a third heart sound gallop, LV enlargement and depressed EF. This information is still pertinent in 1998.

In reviewing all 10 trials as a group,[24-33] we see that duration of follow-up was 4 to 24 weeks; number of patients varied from 12 to 433, with a total of 1058; and no New York Heart Association (NYHA) class IV patients were included. LV ejection fraction was known in 4 trials, fractional shortening in 3, and no LV function data in 3. Vasodilators were used by 0 to 55% of the patients; exercise time increased in 2 of the 10 studies, did not improve in 4, and was unknown in 4.

Summarising the effects in all 1058 patients, heart failure worsened on digoxin therapy in 10% of the patients; however, this value reached 30% in those given placebo. Jaeschke et al.[34] reviewed the same data (but included only 7 studies) and by meta-analysis concluded that 1 in 9 patients with heart failure and sinus rhythm derive a clinically important benefit.

Cardiac related deaths occurred in a total of 12 patients in both the digoxin and placebo groups. However, it should be noted that the clinical event rate was so low in the placebo group, and the duration of follow-up so short, that no conclusions can be drawn regarding mortality in these trials and all previous trials.

On the positive side, these trials showed that digoxin improves LV function and prevents clinical deterioration in some patients, even in mild to moderate heart failure, especially in studies with >100 patients in whom the heart failure is well documented/characterised.

Between 1987 and 1991, 5 randomised, double-blind trials were reported in patients with heart failure in sinus rhythm comparing digoxin with ACE

Table II. Captopril-Digoxin Multicenter Trial[29]

	Captopril (n = 104)	Digoxin (n = 96)	Placebo (n = 100)
Symptoms improved (↓ NYHA Class) [%]	41*	31	22
No. of hospitalisations/ER visits	17	15	29
↑ Exercise time (sec)	82**	54	35
Improved EF (%)	1.8	4.4†	0.9

Abbreviations and symbols: EF = ejection fraction; ER = emergency room; NYHA = New York Heart Association; ↑ = increase; ↓ = decrease; * p < 0.01 *vs.* placebo, ** p < 0.05 captopril *vs* placebo; † p < 0.01 digoxin *vs* placebo and p < 0.05 digoxin *vs* captopril.

inhibitors directly.[35-39] The first trial was reported in 1987 by Alicandri et al.[35] Only 16 patients with NYHA class II-III heart failure were included, with a study duration of only 4 weeks. Exercise time increased in both digoxin (27%) and captopril (35%) groups; no ejection fraction data were provided. This was the first trial to show a decrease in plasma noradrenaline (norepinephrine) levels with digoxin.

The largest trial was the Captopril-Digoxin Multicenter Trial reported in 1988.[29] This included 300 patients (104 on captopril, 96 on digoxin and 100 on a placebo). The captopril dosage goal was 25mg 3 times daily while digoxin dosage ranged from 0.125 to 0.375mg daily. With adjustment of dose, serum digoxin concentration was maintained between 0.7 and 2.5 μg/L. 83% of the patients were male, with an average age of 56.8 years; ischaemic heart disease was the aetiology of heart failure in 62%; average EF was 25%. Most of the patients were NYHA class II or class III heart failure, with no class IV patients. The key results are summarised in table II. Note equal benefit for captopril and digoxin, except digoxin was associated with better EF improvement.

Therefore, by 1992 it was reasonably well proven that digoxin improves exercise tolerance and EF. However, the ACE inhibitor trial data were now accumulating and showing that ACE inhibitors have a major impact on improved survival. Some of the randomised, double-blind, placebo-controlled trials were still inadequate, with incomplete data, an incoherent or inconsistent definition of congestive heart failure was present in some, and there was still no distinction between systolic and diastolic LV dysfunction. These design problems led to the current era and the need for more systematically developed and monitored trials, such as the Prospective Randomised Study of Ventricular Failure and Efficacy of Digoxin (PROVED), Randomised Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE) and Digitalis Investigation Group (DIG) trials.

3. The PROVED Trial of 1993

Even though the PROVED[40] trial is less applicable to clinical medicine and therapy in 1998, since patients on ACE inhibitor therapy were excluded, it should be discussed for comparison with the RADIANCE trial, which was a companion trial with identical methodology except for the concomitant use of an ACE inhibitor.

32 centres randomised 88 patients (digoxin 42, placebo 46) after an 8-week single-blind baseline phase, followed by a 12-week double-blind withdrawal phase.[40] Each centre enrolled 1 to 11 patients (median 2), 29 enrolling fewer than 4 patients. Baseline data are outlined in table III.

Table III. Key baseline data of PROVED[40] and RADIANCE[41] trials

	PROVED	RADIANCE
No. of patients randomised	88	178
Age (y)	64 ± 2	60
Men/women	75/13	136/42
NYHA class II/III	73/14	130/48
LVEF (%)	27-29	26-28
LVED dimension (mm)	67 ± 1	68
Cardiomyopathy (%)		
ischaemic	63	57
primary	37	36
Serum digoxin concentration (μg/L)	1.1-1.2	1.1-1.2
Digoxin dosage (mg/day)	0.375	0.37-0.40

Abbreviations: LVED = left ventricular end diastolic; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PROVED = Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin trial; RADIANCE = Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme trial.

Table IV. Treatment failures in the PROVED[40] and RADIANCE[41] trials. Figures in parentheses are percentage of total of patients in each arm

	PROVED		RADIANCE	
	placebo	digoxin	placebo	digoxin
	n = 46	n = 42	n = 93	n = 85
Increased need for diuretics	10 (22)	4 (10)	11 (12)	2 (2)
ER visits for CHF	6 (13)	3 (7)	3 (3)	0
Hospitalisation for CHF	1 (2)	0 (0)	9 (10)	2 (2)
Death	1 (2)	1 (2)	0	2 (2)
Total	18 (39)	8 (19)	23 (25)	6 (7)

Abbreviations: CHF = congestive heart failure; ER = emergency room; PROVED = Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin trial; RADIANCE = Randomized Assessment of Digoxin on Inhibitors of the Angiotensin-Converting Enzyme trial.

Significant worsening of exercise duration occurred at 12 weeks in patients on placebo (median decrease of 96 seconds) versus a slight increase in exercise duration measured in patients on digoxin (4.5 seconds, $p = 0.003$); however, no significant difference was documented by the 6-minute walk test. LV ejection fraction changes were small but statistically significant: baseline EF in the placebo group was $29 \pm 2\%$ and decreased to $26 \pm 2\%$; baseline EF was $27 \pm 1\%$ in the digoxin group and increased to $29 \pm 2\%$, $p = 0.016$. A smaller number of treatment failures was reported in the digoxin group (table IV). No clinical digoxin toxicity was identified.

4. The RADIANCE Study of 1993

43 centres in the US and Canada randomised 178 patients (placebo 93, digoxin 85) with New York class II to class III heart failure, EF <35%, LV end diastolic dimension per echocardiograph >60mm and exercise duration by the modified Naughton protocol 2 to 14 minutes, despite treatment with an ACE inhibitor, diuretic and digoxin for 3 months.[41] See table III for key baseline characteristics. Treatment failures are summarised in table IV. Only 1 episode of digoxin toxicity occurred.

The placebo group deteriorated and the digoxin group remained stable with regard to exercise tolerance by maximal treadmill time, with a difference of 43 seconds between the groups, $p = 0.033$. Utilising the 6-minute walk test, a similar result was observed with a difference of 41m, $p = 0.01$.

On the other hand, objective changes in the cardiac/thoracic ratio per chest x-ray and the LV size and function data by echocardiography were not impressive for the digoxin group. Specifically, LV ejection fraction decreased in the placebo group from 30 to 26% versus 27 to 26% in the digoxin group. LV end diastolic dimension per echocardiograph increased in the placebo group from 66 to 68mm; the digoxin group changed from 69 to 68mm. Including both the PROVED and RADIANCE trials, it does appear that an objective benefit of digoxin is real for improvement of symptoms and exercise duration, and further, that digoxin prevents deterioration of ejection fraction. The RADIANCE trial, with use of an ACE inhibitor, supports a continuing role for digoxin in current clinical practice, even in patients with only class II or mild congestive heart failure. Further, it should be noted that the dose of digoxin in both the PROVED and RADIANCE trials was a mean of 0.375mg, which is high by 1998 standards. Mortality data were still totally incomplete and unknown, which led to the DIG Trial.

5. The DIG Trial of 1997

The DIG trial was a pure morbidity and mortality trial, with no exercise tolerance data and no follow-up ejection fractions.[42]

302 clinical centres in the US and Canada randomised 6800 patients (3397 digoxin, 3403 placebo), with a mean follow-up period of 37 months (range 28 to 58 months). On final analysis, 94% of the patients were taking an ACE inhibitor and

Table V. Baseline data from the Digitalis Investigation Group (DIG) trial[42]

	Placebo (n = 3403)	Digoxin (n = 3397)
Age (y)	64.0	63.8
Female (%)	24.7	24.7
Race, nonwhite (%)	14.6	14.3
EF (%)	31.9	32.0
NYHA class (%)		
I	14.0	14.4
II	54.8	54.1
III	29.3	29.5
IV	1.9	2.0
History of (%)		
myocardial infarct	64.7	65.3
current angina	27.1	26.4
hypertension	45.0	45.8

Abbreviations: EF = ejection fraction; NYHA = New York Heart Association.

81.5% a diuretic. Key baseline data are summarised in table V.

In the digoxin group, 17, 70 and 10.5% of patients received daily doses of 0.125mg, 0.25mg and 0.375mg, respectively. The allowed target serum digoxin concentration was wide (0.5 to 2.0 μg/L), which complicates interpretation of trial results.

No difference was found in all-cause mortality between digoxin and the placebo group (see table VI). In addition, no difference was documented in overall cardiovascular mortality. However, there was a strong trend to less mortality from worsening heart failure in the digoxin group ($p = 0.06$). Some concern was raised by 'other cardiac' mortality figures, which possibly referred to a cardiac arrhythmia: 508 digoxin patients (15%) versus 444 placebo patients (13%) [relative risk (rr) = 1.14; 95% confidence interval (CI) 1.01 to 1.30]. Yet this was not confirmed by the number of patients with cardiovascular hospitalisations, documented ventricular arrhythmia and cardiac arrests: 142 digoxin recipients versus 145 placebo patients.

The number of patients hospitalised for cardiovascular reasons, especially for worsening heart failure, was significantly less in the digoxin group ($p < 0.001$). No difference was identified in the incidence of myocardial infarction, unstable angina or coronary revascularisations. The risk of death from any cause and hospitalisation for worsening heart failure was significantly lower in the digoxin group (rr = 0.85; 95% CI 0.79 to 0.91). Combining the risk of death and/or hospitalisation secondary to worsening heart failure showed that the digoxin rate was significantly lower ($p < 0.001$; rr = 0.75, 95% CI 0.69-0.82).

Subset analysis is demonstrated in table VII. Noteworthy is the fact that the effect of digoxin is greater in patients with nonischaemic cardiomyopathy, EF <25%, larger heart size and more symptomatic class III-IV status. However, digoxin was still effective in the 25 to 45% EF group, and in those with ischaemic aetiology, smaller heart size and NYHA class I-II status.

Table VI. Digitalis Investigation Group (DIG) trial.[42] Figures in parentheses are percentage of total in each arm or 95% confidence intervals (CI)

	Placebo (n = 3403)	Digoxin (n = 3397)	Relative risk
Cause of Death			
All	1194 (35.1)	1181 (34.8)	0.99
Cardiovascular	1004 (29.5)	1016 (29.9)	1.01
Worse CHF	449 (13.2)	394 (11.6)	0.88 (0.77-1.01)
Reason for hospitalisation			
No. of patients hospitalised	2282 (67.1)	2184 (64.3)	0.92 (0.87-0.98)
Cardiovascular	1850 (54.4)	1694 (49.9)	0.87 (0.81-0.93)
Worse CHF	1180 (34.7)	910 (26.8)	0.72 (0.66-0.79)
Ventricular arrhythmia, cardiac arrest	145 (4.3)	142 (4.2)	

Abbreviations: CHF = congestive heart failure.

Table VII. Digitalis Investigation Group (DIG) trial[42] subset data: effect of digoxin on the frequency of death or hospitalisation due to worsening congestive heart failure. Figures in parentheses are percentage of total in each arm or 95% confidence intervals (CI)

	Placebo	Digoxin	Relative risk
Total trial			
Ejection fraction			
0.25-0.45%	735/2273 (32.3)	613/2270 (27.0)	0.80 (0.72-0.89)
<0.25%	556/1130 (49.2)	428/1127 (38.0)	0.68 (0.60-0.77)
Cause of heart failure			
ischaemic	873/2398 (36.4)	731/2405 (30.4)	0.79 (0.72-0.88)
nonischaemic	413/996 (41.5)	301/983 (31.1)	0.67 (0.58-0.77)
Cardiothoracic ratio			
<0.55	624/2233 (32.4)	600/2220 (27.0)	0.79 (0.71-0.88)
>0.55	567/1170 (48.5)	441/1176 (37.5)	0.69 (0.61-0.78)
NYHA class			
I-II	739/2296 (32.2)	601/2275 (26.4)	0.78 (0.70-0.87)
III-IV	552/1105 (50.0)	438/1118 (39.2)	0.70 (0.61-0.79)
Ancillary trial			
Deaths	116/496	115/492	

Abbreviations: NYHA = New York Heart Association.

Reassuringly, the ancillary trial of 988 patients with diastolic dysfunction (EF >45%) showed no increased death rate with digoxin therapy, which was a significant concern of clinicians. In addition, the combined death rate and hospitalisations secondary to worsening heart failure showed a definite trend in favour of digoxin: rr = 0.82; 95% CI 0.63 to 1.07.

It is pertinent to note that 45% of this entire trial was made up of patients with a history of systemic hypertension, and the cause of heart failure was designated as hypertensive heart disease in 8.0 to 9.2% of the total group. Therefore, we can postulate that a significant number of these hypertensive patients are in the ancillary trial, which would explain the percentage of patients with diastolic dysfunction, but those data are not available for review. No neurohormonal data were measured in either the total or ancillary trial patients.

In summary, reviewing all previous clinical trials, we feel that the clinician can be comfortable in utilising digoxin in congestive heart failure with normal sinus rhythm. It does not improve survival, but it will prevent symptomatic deterioration, improve exercise tolerance and reduce the hospitalisation rate and the increased cost of hospitalisation.

In addition, digoxin is the first inotropic agent shown not to worsen survival, even in patients with diastolic dysfunction. Possible reasons why digoxin does not have an increased mortality rate, as do other inotropes, are as follows:

1. Different mechanism of action at the cellular level.

2. Most inotropes downregulate the β receptors, while digoxin has the potential advantage of upregulating β receptors.[4]

3. The neuromodulator effect of digoxin (decreased sympathetic activity with more dominant parasympathetic action).

6. Inotrope Versus Neurohormonal Modulator

Digitalis has been shown to increase the rate of rise in intraventricular pressure during isovolumic systole while maintaining a constant heart rate and aortic pressure. In the 1960s, Sonnenblick et al.[43] showed that digitalis shifted the force-velocity curve upwards and to the right in the isolated cardiac muscle preparation. Bedside correlation shows a shifting of the LV function curve (Frank-Starling) upwards and to the left, so that more stroke work and cardiac output is generated by a given LV end diastolic pressure.

As mentioned above, Poole-Wilson and Robinson[4] suggested that digitalis has only a 'small' inotropic effect. Braunwald[44] and Van Veldhuisen et al.[45] have recently written that digoxin stimulates myocardial contractility 'moderately'. Rahimtoola and Tak[46] recently summarised the beneficial haemodynamic benefits of digoxin:

- at rest–decreased right atrial and wedge pressure and increased cardiac output; and
- exercise-decreased RA and wedge pressure, increased C0 and LV stroke–work index.

Probably the best recent study utilising intravascular measurements was by Gheorghiade et al.[47] with their intravascular study of 11 patients. In 6 of 11 patients the cardiac index increased with the IV administration of digoxin 1mg from 2.6 ± 0.7 L/min/m^2 to 3.3 ± 0.6 L/min/m^2; pulmonary capillary wedge pressure decreased from 24 ± 7 to 17 ± 4mm Hg; and LV ejection fraction increased from 21 ± 13% to 29 ± 11%. It is noteworthy that the responsive patients had more severe heart failure, with a third sound gallop and lower EF.

However, with review of published trials, with emphasis on the Captopril-Digoxin and RADIANCE trials, documentation of improved ejection fraction is not that impressive with digoxin. It also appears that this inotropic effect is mainly observed at higher digoxin doses such as 0.375mg per day.

The neurohormonal data with digoxin started with the publication of a small study of 16 patients by Alicandri et al. in 1987.[35] They were the first to show a decrease in plasma noradrenaline level with digoxin. In the background was also a growing database from ACE inhibitor trials and improved survival, which clearly supported the neurohormonal hypothesis.[48] More recently, the newer data with β-blocking drugs, especially carvedilol,[49] have supported the improved survival with both blunting of the renin-angiotensin aldosterone and sympathetic nervous systems.

Ferguson and colleagues[50,51] first demonstrated direct suppression of sympathetic nerve activity by digoxin in human skeletal muscle. Two studies reported in 1995 (Krum et al.[52] and Brouwer et al.[53]) showed an improvement in autonomic function by improved heart rate variability measurements, in essence causing a decreased sympathetic and increased parasympathetic effect, which is the desired result. A lower heart rate with more variable RR intervals on the ECG correlates with better survival. In addition, Krum et al.[52] showed that the plasma noradrenaline level decreased significantly after digoxin from 552 ± 80 to 390 ± 37 μg/L (42%) [$p < 0.05$]. Decrease in plasma noradrenaline was greatest in patients who had the highest level before treatment.

The Dutch Ibopamine Multicenter Trial (DIMT) studied 161 patients, 80% of whom were in NYHA class II status, for 6 months with either ibopamine (n = 53), digoxin (n = 55) or placebo (n = 53).[54] After 6 months, plasma noradrenaline level increased in the placebo group (+62 ng/L, p = 0.018), but decreased in the digoxin group (–106 ng/L, p = 0.004). The ibopamine group showed no significant change (–13 ng/L).

What is the mechanism of the neurohormonal modulation? The usual explanation is improvement of the impaired baroreceptor reflexes in heart failure, again with the end result of decreased sympathetic and improved vagal/parasympathetic activity. But it appears that it is not just enhanced vagal tone secondary to improved haemodynamic status, since direct recording of sympathetic nerve activity shows a rapid decrease in sympathetic activity preceding observed haemodynamic actions.[49] Possible explanations of digoxin activity put forward to explain the increased parasympathetic activity measured after administration include: (a) increased sensitivity of arterial baroreceptor reflex, i.e. augmentation of afferent signals; (b) a central action to increase efferent vagal signals; (c) an alteration of the electrical excitability of efferent vagal fibres and impulse transmission in autonomic ganglia; and (d) an increase in the sensitivity of cardiac fibres to acetylcholine.[55]

Thus, the discussion centres around whether digoxin is predominantly an inotrope, a neurohormonal modulator, or both. The final answer regarding dominance or how much of each is unknown. The best answer is probably that by Gheorghiade et al.,[56] in which they postulate that 'it is possible that low dose digoxin attenuates the neurohormonal activation without improving the haemodynamics, whereas a higher dose improves

haemodynamics without having a modulating effect on neurohormones'.

7. Is a Higher Digoxin Dose Necessary?

First, it is well known from the pre–ACE inhibitor therapy era, when larger doses of digoxin were utilised, that the incidence of digitalis toxicity was much higher and problematic. Currently, when digoxin dosages of 0.125 to 0.25 mg/day are utilised, recognised clinical digoxin toxicity is much less common but no dose-response curve has ever been established in the intact human heart with normal sinus rhythm.

It should be remembered that in the PROVED and RADIANCE trials, the mean dosage of digoxin was 0.375 mg/day. However, Gheorghiade et al.[56] performed a study on a subset of the RADIANCE trial patients and their report is pertinent to the argument that a lower dosage may be all that is necessary. In their study of 18 patients, increasing the mean daily digoxin dose from 0.2 ± 0.7 to 0.39 ± 0.11 mg increased mean serum digoxin concentrations from 0.67 ± 0.22 to 1.22 ± 0.35 μg/L. 3 patients took 0.25 mg/day, 8 received 0.375 mg/day and 7, 0.5 mg/day. With the higher dosages, LV ejection fraction increased from 23.7 ± 9.6 to 27.1 ± 11.8%, p = 0.007. However, no significant clinical improvement was documented with no improvement in the heart failure score or exercise time (or serum noradrenaline levels), although it must be noted that only 18 patients were studied.

Slatton et al.[57] recently described their experience with 19 men aged 64 ± 12 years; 13 patients were NYHA class II and 6 were class III, with a mean EF of 28 ± 9% (range 14 to 43%). 18 of 19 patients were on an ACE inhibitor, 1 patient was taking a hydralazine and isosorbide dinitrate combination, and 17 of 19 patients were receiving a diuretic. No digoxin had been utilised for the previous 3 months. The patients then were given digoxin 0.125mg for 2 weeks, followed by 0.25mg for 2 weeks. Heart rate decreased from 87 beats/min at baseline to 82 and 81 beats/min in those on the 0.125mg and 0.25mg dosages, respectively. No significant change occurred in LV end diastolic dimension by echocardiography. However, when percentage fractional shortening was corrected for heart rate and adjusted for end systolic wall stress, significant improvement (upwards shift) occurred with the lower dosage but no further improvement was associated with the 0.25mg dosage. No significant change occurred in plasma noradrenaline levels with either dosage. They concluded that digoxin 0.25mg daily provided no additional haemodynamic or autonomic benefit over 0.125mg daily in patients with mild-to-moderate heart failure.

At a recent meeting of the International Society of Heart Failure, Gheorghiade[58] reported the preliminary results of the DIG trial substudy: a correlation of increased serum digoxin concentrations with increased mortality. Specifically, when serum digoxin concentrations were <1.0 μg/L, mortality was 30%; concentrations >2.0 μg/L showed a mortality of 63%. No renal function or age data were available. It should be emphasised that these data are more hypothesis-generating than conclusive.

In addition, subanalysis of the Prospective Randomised Milrinone Survival Evaluation (PROMISE) study showed that serum digoxin concentrations >1.1 μg/L were highly predictive of increased mortality compared with concentrations of less than 1.1 μg/L.[59]

Therefore, in agreement with earlier trial data, higher digoxin doses provide improved haemodynamic results without effect on serum noradrenaline levels. Moreover, the higher the dosage and serum digoxin concentration, the higher the risk and potential mortality. Our interpretation is that the average dosage utilised today should be 0.25 mg/day for the average-sized patient under the age of 65, and 0.125 mg/day for the smaller, older patient with poorer renal function (serum creatinine >1.5 mg/dl).

8. Should Digoxin Be Used in Only Moderate To Severe Heart Failure?

A review of the current clinical practice guidelines as published by the US Agency for Healthcare

Policy and Research (AHCPR) in 1994[60] reached the following conclusions:

1. Digoxin can prevent clinical deterioration of patients with heart failure and improve patients' symptoms (strong evidence on literature review).

2. Digoxin should be used routinely in patients with severe heart failure, and added to the therapy of patients with mild to moderate failure who remain symptomatic after optimal management with ACE inhibitors and diuretics (strength of evidence on literature review much weaker). The data reviewed included the RADIANCE trial but not the DIG trial, in which it will be recalled that digoxin showed greater effect in NYHA class III-IV patients, but still elicited a significant improvement even in the NYHA class I-II patients. The PROVED, RADIANCE and DIG trials all included >50% class II or mildly disabled patients. The DIMT investigators also showed a positive benefit with digoxin as monotherapy in mild heart failure.[61]

The American College of Cardiology/American Heart Association Task Force Report on Guidelines for Evaluation of Management of Heart Failure was published in November, 1995.[62] Their conclusion with strong evidence was that digoxin should be used in patients who do not adequately respond to ACE inhibitors and diuretics. Moderate evidence was found in the literature for digoxin use in all patients with heart failure due to systolic dysfunction.

9. Conclusion

In summary, we can conclude that even NYHA class II patients with mild congestive heart failure secondary to LV systolic dysfunction and normal sinus rhythm have documented benefit by digoxin therapy.

In our clinical practice, we currently use digoxin for heart failure patients as follows:

- LV diastolic dysfunction: digoxin is empirically still contraindicated, but the ancillary substudy of the DIG trial is reassuring, showing no increase in mortality; and
- Chronic LV systolic dysfunction with normal sinus rhythm: ACE inhibitor therapy should always be first and foremost. In patients with moderate to severe symptoms, large left ventricle and EF <40%, especially with third sound gallop, clinical trial data strongly support digoxin use. In patients with mild heart failure, an ACE inhibitor is the first choice but digoxin is still a reasonable additive if the patient remains symptomatic. Our practice is to use a daily dose of digoxin in the range of 0.125 to 0.25mg.

References

1. Withering, W. An account of the foxglove and some of its medical uses, with practical remarks on dropsy, and other diseases. In: Woolliest FA, Keys TE, editors. Classics of cardiology. New York: Henry Schuman, Dover Publications, 1941: Vol. 1: 231-52
2. Christian HA. Digitalis effects in chronic cardiac cases with regular rhythm in contrast to auricular fibrillation. Med Clin North Am 1922; 5: 117-9
3. Hollman A. American College of Cardiology ACCEL tape, 1997 Jun
4. Poole-Wilson P, Robinson K. Digoxin – a redundant drug in congestive cardiac failure. Cardiovasc Drugs Ther 1989; 2: 733-41
5. Weber KT. Heart failure: lessons learned over the past 25 years. Clin Cardiol 1995; 18: 123-30
6. Gheorghiade M, Zarowitz BJ. Review of randomized trials of digoxin therapy in patients with chronic heart failure. Am J Cardiol 1992: 48G-62G
7. Tauke J, Goldstein S, Gheorghiade M. Digoxin for chronic heart failure: a review of the randomized controlled trials with special attention to the PROVED and RADIANCE Trials. Prog Cardiovasc Dis 1994; 37: 49-58
8. Gheorghiade M. Digoxin. In: Crawford MH, editor. Cardiology Clinics: annual drug therapy. Philadelphia (PA): WB Saunders, 1997; volume 1: 81-103
9. Starr I, Luchi RJ. Blind study of the action of digitoxin on elderly women. Am Heart J 1969; 78: 740-51
10. Dall JLC. Maintenance digoxin in elderly patients. BMJ 1970; 2: 705-6
11. Kirsten E, Rodstein M, Iuster Z. Digoxin in the aged. Geriatrics 1973; 1: 95-101
12. Fonrose HA, Ahlbaum N, Bugatch E, et al. The efficacy of digitalis withdrawal in an instructional aged population. J Am Geriatr Soc 1974; 22: 208-11
13. Hull SM, MacKintosh A. Discontinuation of maintenance digoxin therapy in general practice. Lancet 1977; 2: 1054-5
14. Johnston GD, McDevitt DG. Is maintenance digoxin necessary in patients with sinus rhythm? Lancet 1979; I: 567-70
15. McHaffie D, Purcell H, Mitchell-Heggs P, et al. The clinical value of digoxin in patients with heart failure and sinus rhythm. Q J Med 1978; 47: 401-19
16. Krakauer R, Petersen B. The effects of discontinuing maintenance digoxin therapy. Dan Med Bull 1979; 26: 10-3
17. Hutcheon D, Memeth E, Quinlan D. The role of furosemide alone and in combination with digoxin in the relief of symp-

toms of congestive heart failure. J Clin Pharmacol 1980; 20: 59-68
18. Arnold SB, Bird RC, Meister W, et al. Long-term digitalis therapy improves left ventricular function in heart failure. N Engl J Med 1980; 303: 1443-8
19. Sommers DeK, Reitz CJ, Koch Z, et al. Digoxin withdrawal with patients in sinus rhythm. S Afr Med J 1981; 60: 239-40
20. Murray RG, Tweddel AC, Martin W, et al. Evaluation of digitalis in cardiac failure. BMJ 1982; 284: 1526-8
21. Griffiths BE, Penny WJ, Lewis MJ, et al. Maintenance of the inotropic effects of digoxin on long-term treatment. BMJ 1982; 284: 1819-22
22. Gheorghiade M, Beller GA. Effects of discontinuing maintenance digoxin therapy in patients with ischemic heart disease and congestive heart failure in sinus rhythm. Am J Cardiol 1983; 51: 1243-50
23. Yusuf S, Garg R, Held P, et al. Need for a large randomized trial to evaluate the effects of digitalis on morbidity and mortality in congestive heart failure. Am J Cardiol 1992; 69: 64G-70G
24. Dobbs SM, Kenyon WI, Dobbs RJ. Maintenance digoxin after an episode of heart failure: placebo-controlled trial in outpatients. BMJ 1977; 1: 749-52
25. Fleg JL, Gottlieb SH, Lakatta EG. Is digoxin really important in treatment of compensated heart failure? Am J Med 1982; 73: 244-50
26. Lee C, Johnson RA, Bingham GB, et al. Heart failure in outpatients. N Engl J Med 1982: 306: 699-705
27. Taggart AJ, Johnston GD, McDevitt DG. Digoxin withdrawal after cardiac failure in patients with sinus rhythm. J Cardiovasc Pharmacol 1983: 5: 229-34
28. Guyatt GH, Sullivan MJ, Fallen EL, et al. A controlled trial digoxin in congestive heart failure. Am J Cardiol 1988; 61: 371-5
29. Captopril-Digoxin Multicenter Research Group. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. JAMA 1988; 259: 539-44
30. German and Austrian Xamoterol Study Group. Double blind placebo-controlled comparison of digoxin and xamoterol in congestive heart failure. Lancet 1988; I: 489-93
31. Dibianco R, Shabetai R, Kostuk W, et al. A comparison of oral milrinone, digoxin, and their combination in treatment of patients with chronic heart failure. N Engl J Med 1989; 320: 677-83
32. Pugh SE, White NJ, Arnson JK, et al. Clinical, hemodynamic, and pharmacological effects of withdrawal and reintroduction of digoxin in patients with heart failure in sinus rhythm after long term treatment. Br Heart J 1989; 61: 529-39
33. Fleg JL, Rothfeld B, Gottlieb SH, et al. Effect of maintenance digoxin therapy on aerobic performance and exercise left ventricular function in mild to moderate heart failure due to coronary artery disease: a randomized, placebo-controlled crossover trial. J Am Coll Cardiol 1991; 17: 743-51
34. Jaeschke R, Oxman AD, Guatt GH. To what extent do congestive heart failure patients in sinus rhythm benefit from digoxin? A systematic review and meta-analysis. Am J Med 1990: 88: 279-86
35. Alicandri C, Fariello R, Boni E, et al. Captopril versus digoxin in mild-moderate chronic heart failure: a crossover study. J Cardiovasc Pharmacol 1987; 9: S61-7
36. Beaune J. Comparison of enalapril versus digoxin for congestive heart failure. Am J Cardiol 1989; 63: 22D-5D
37. Kromer EP, Elsner D, Riegger GAJ. Digoxin, converting-enzyme inhibition (quinapril), and the combination in patients with congestive heart failure functional class II and sinus rhythm. J Cardiovasc Pharmacol 1990; 16: 9-14
38. Davies RF, Beanlands DS, Nadeau C, et al. Enalapril versus digoxin in patients with congestive heart failure: a multicenter study. J Am Coll Cardiol 1991; 18: 1602-9
39. Drexler H, Schumacher M, Siegrist J, et al. Effect of captopril and digoxin on quality of life and clinical symptoms in patients with coronary artery disease and mild heart failure [abstract]. J Am Coll Cardiol 1992; 19: 260A
40. Uretsky BF, Young JB, Shahidi FE, et al. Randomized study assessing the effect of digoxin withdrawal in patients with mild to moderate chronic congestive heart failure. J Am Coll Cardiol 1993; 22: 955-62
41. Packer M, Gheorghiade M, Young JB, et al. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. N Engl J Med 1993; 329: 1-7
42. Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med 1997; 336: 525-33
43. Sonnenblick EH, Williams JF, Glick G, et al. Studies on digitalis: XV. Effects of cardiac glycosides on myocardial force-velocity relations in the nonfailing human heart. Circulation 1966; 34: 532-9
44. Braunwald E. In: Isselbacher KJ, Wilson JD, Martin JB, et al. Harrison's Principles of internal medicine. 14th ed. New York: McGraw-Hill, 1998: 1294-5
45. Van Veldhuisen DJ, DeGraeff PA, Remme WJ, et al. Value of digoxin in heart failure and sinus rhythm: new features of an old drug? J Am Coll Cardiol 1996; 28: 813-9
46. Rahimtoola SH, Tak T. The use of digitalis in heart failure. Curr Prob Cardiol 1996; 32: 826-7
47. Gheorghiade M, St Clair J, St Clair C, et al. Hemodynamic effects of intravenous digoxin in patients with severe heart failure initially treated with diuretics and vasodilators. J Am Coll Cardiol 1987; 9: 849-57
48. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992; 20: 248-54
49. Packer M, Bristow MR, Cohn JN, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996; 334: 1349-55
50. Ferguson D, Berg WJ, Sanders JS, et al. Sympathoinhibitory responses to digitalis glycosides in heart failure patients: direct evidence from sympathetic neural recordings. Circulation 1989; 80: 65-77
51. Ferguson DW. Digitalis and neurohormonal abnormalities in heart failure and implications for therapy. Am J Cardiol 1992; 69: 24G-32G
52. Krum H, Bigger JT, Goldsmith RL, et al. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. J Am Coll Cardiol 1995; 25: 289-94
53. Brouwer J, Van Veldhuisen DJ, Veld AJM, et al. Heart rate variability in patients with mild to moderate heart failure: effects of neurohormonal modulation by digoxin and ibopamine. J Am Coll Cardiol 1995; 26: 983-90
54. Van Veldhuisen DJ, Veld AJM, Dunselman PHJM, et al. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMT). J Am Coll Cardiol 1993; 22: 1564-73
55. Marcus F. Digitalis. In: Singh BN, Dzau VJ, Van Houtte PM, et al., editors. Cardiovascular pharmacology and therapeutics. New York: Churchill Livingston, 1994: 345

56. Gheorghiade M, Hall VV, Jacobsen G, et al. Effects of increasing maintenance dose of digoxin on left ventricular function and neurohormones in patients with chronic heart failure treated with diuretics and angiotensin-converting enzyme inhibitors. Circulation 1995; 92: 1801-7
57. Slatton ML, Irani WN, Hall SA, et al. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure in normal sinus rhythm? J Am Coll Cardiol 1997; 29: 1206-13
58. Gheorghiade M. Serum digoxin doses below 1ng/mL held safer [interview]. Intern Med News, 1997 Aug 15
59. Mancini DM, Benotti JR, Elkayam U, et al. Antiarrhythmic drug use and high serum levels of digoxin are independent adverse prognostic factors in patients with chronic heart failure [abstract]. Circulation 1991; 84 Suppl. II: 243
60. Agency for Health Care Policy and Research. Clinical Practice Guideline No. 11. Heart failure: evaluation and care of patients with left ventricular systolic dysfunction. Rockville (MD): US Department of Health and Human Services, 1994: publication no. 94-0612
61. Van Veldhuisen DJ, Brouwer J, Veld AJM, et al. Progression of mild untreated congestive heart failure during 6 months followup and clinical and neurohormonal effects of ibopamine and digoxin as monotherapy. Am J Cardiol 1995; 75: 796-800
62. ACC/AHA Task Force Report. Guidelines for the evaluation and management of heart failure. J Am Coll Cardiol 1995; 26: 1376-98

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