

Digitalis Medication in Treatment of Heart Failure

José Fernando Guadalajara-Boo

National Institute of Cardiology “Ignacio Chávez”, Mexico City, Mexico

Email: guadalajara@cardiologia.org.mx

How to cite this paper: Guadalajara-Boo, J.F. (2024) Digitalis Medication in Treatment of Heart Failure. *Chinese Medicine*, 15, 1-13.

<https://doi.org/10.4236/cm.2024.151001>

Received: September 20, 2023

Accepted: January 8, 2024

Published: January 11, 2024

Copyright © 2024 by author(s) and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

In Mexico, digitalis was known since the 16th century and was used to treat patients with bloating, and it was not until the 20th century that it began to be used as a medicine for heart failure. In conjunction with diuretics. Digitalis was later used in combination individualized with the new medications, for this purpose and research has shown that the combination of medications on an individualized basis is what is currently successfully available for the medical treatment of heart failure.

Keywords

Digitalis, Heart Failure

1. Introduction

Origin in the Use of Digital Medication

Digitalis medication has been used for more than 200 years as a treatment initially for patients who had partial or total fluid retention.

CODICE BADIANO

YOLOXOCHILT (HEART FLOWER) (Figure 1)

The word Yolloatl means “life force” and the sun for the indigenous according to the worldview of the mexicas works in the universe the same that the heart in the human, both they are responsible for maintaining life. The first book about a topic related to Cardiology was the “Book about the medicinal herbs of the Indians (Libellus of Medicine libus indorum herbis) made by Martín de la Cruz at the Santiago Tlatelolco School 1551, in which he not only described the effects of various medicinal plants but it was also illustrated by botanical drawings of the plants studied.

This work was written in Nahuatl language and translated into Latin by Juan



Figure 1. Yolloxochitl flower.

Badiano for what is known as “CODICE BADIANO”, it is emphasized that really the author was Martín de la Cruz. In this book describes charitable actions about the heart of Yolloxochitl (first description of a plant with digitalis action).

This work traveled through Peru, Madrid, Paris, Rome, the Library Windsor Royal in England and from there to the Vatican, where was preserved until than the original text was gifted by him Pope Juan Pablo II to Mexican state in 1990 and now the work rests in the of National Museum Anthropology, Mexico City [1].

Digitalis medication (**Figure 2**), began to be used in Mexico in the 19th century, but it was not until the beginning of the 20th century (1920) that Dr. Ignacio Chávez in Mexico systematized its use and in his professional medical thesis, he wrote the results obtained, which in conclusion were that digitalis medication is useful in heart failure in small doses and it is not appropriate to give it when the heart did not need tonics [2].

2. Scientific Research of Digitalis Medication

In 1961 Braunwald experimentally demonstrated the positive inotropic effect on isolated myofibrils. (**Figure 3**) [3]; later, in 1964, Dean T. Mason demonstrated how digitalis, with its inotropic effect, significantly improves cardiac output and tissue perfusion, and at the same time blocks adrenergic action, producing arteriole and venous dilation, thereby reducing afterload and preload, which is followed by a marked clinical improvement in patients with HF quantitatively increasing blood flow, reducing peripheral resistance, as well as central venous pressure and heart rate [4] (**Figure 4**); effects that are opposite when digitalis is administered to subjects who do not have HF (with normal systolic function (SF) since increases them peripheral resistanc, cardiac output and blood flow whitout change (**Figure 5**), facts that show that the digitalis effect is only useful in patients with HF and are counterproductive when administered to patients with normal SF [2] [4], facts that corroborate the clinical observations made 40 years earlier by Professor Chávez [2]. This digitalis effect is demonstrated by Vatner and Braunwald in 1974 (**Figure 6**), by administering intravenous Ouabain to dogs with HF, the dp/dt increased very significantly, an effect that was insignificant and of very short duration in dogs with normal cardiac function,

HISTORY OF CARDIOLOGY IN THE MURALS OF DIEGO RIVERA NATIONAL INSTITUTE OF CARDIOLOGY
 "IGNACIO CHAVEZ", MEXICO

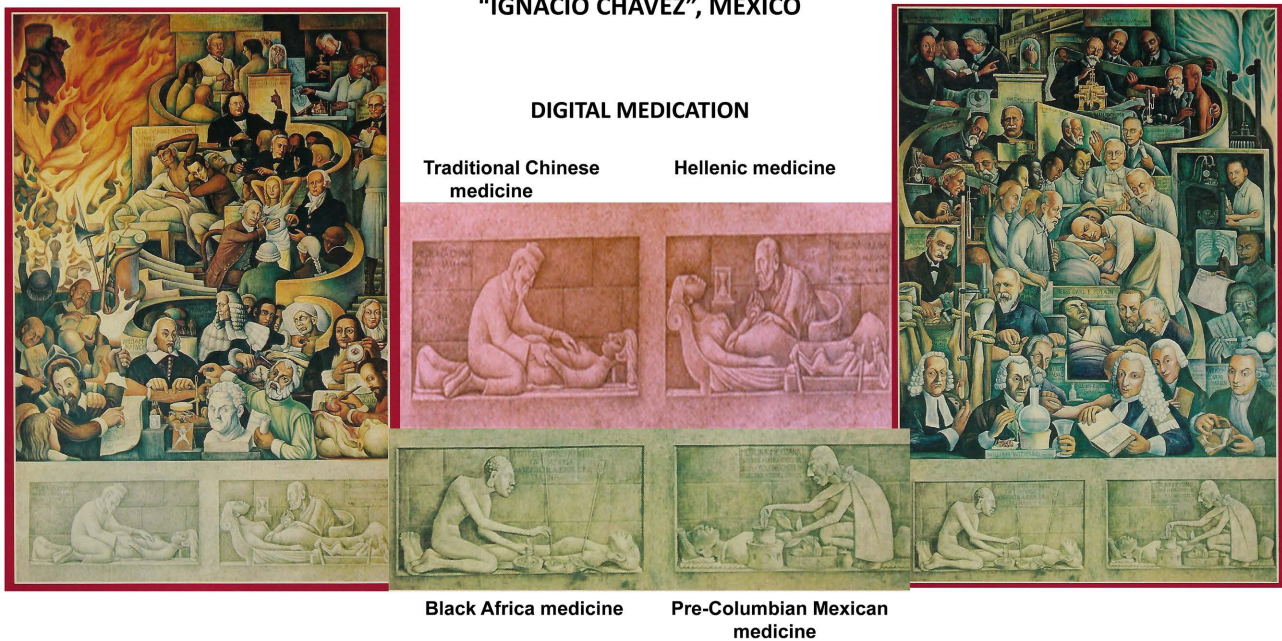


Figure 2. Representation of digitalis plant in various parts of the world.

Effect of Ouabain in Myocardial Contractility

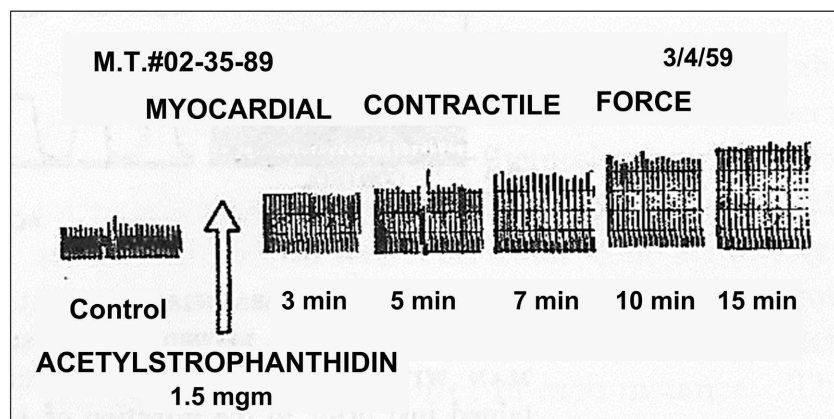


Figure 3. The contractile force increased 89% in normal myofibrils with Ouabain in relation to the basal conditions.

with which it also show that digitalis drugs are useful in the failing heart, but not in the normally functioning heart [5].

It is important to emphasize that digitalis is the only inotropic drug that reduces myocardial oxygen consumption (MVO_2) in HF.

The balance between its determinants is favorably affected: increased contractility, decrease heart rate, wall stress (pre- and afterload) which reduces MVO_2 and the bottom line is that the inotropic effect is accompanied by a decrease in MVO_2 [6] [7] (Figure 7); I emphasize that digitalis is the only inotrope that has this effect.

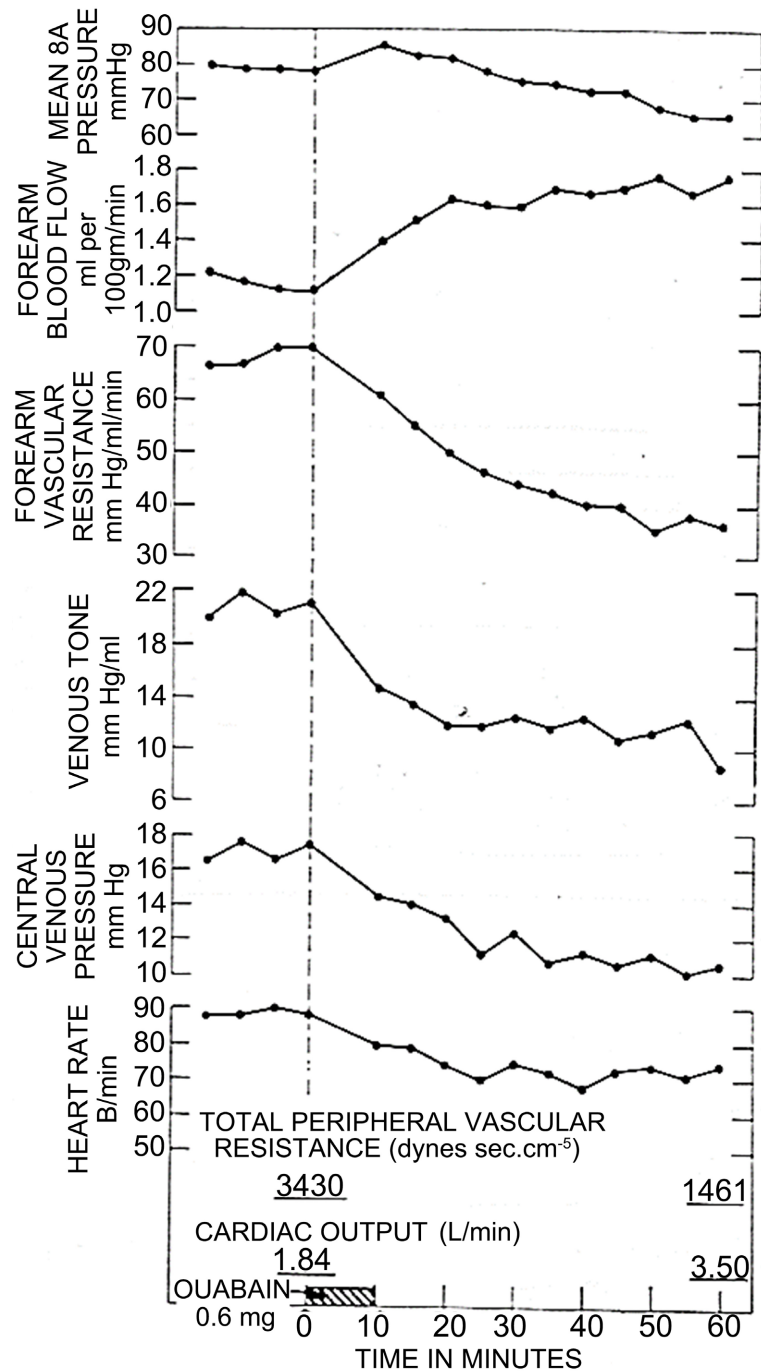


Figure 4. Peripheral effect and cardiac output of digitalis in patients with heart failure (3).

3. Digitalis Medication in Acute Heart Failure (Figure 8)

52-year-old patient with acute myocardial infarction and pulmonary edema due to acute heart failure. **Figure 8(A)** shows a patient with intense dyspnea, audible crackles at a distance and “Salmony” expectoration. **Figure 8(B)** shows the ECG with tachycardia of 150 × min., Acute myocardial infarction in anteroapical evolution with high lateral extension, digoxin, furocemide, spironolactone, IV

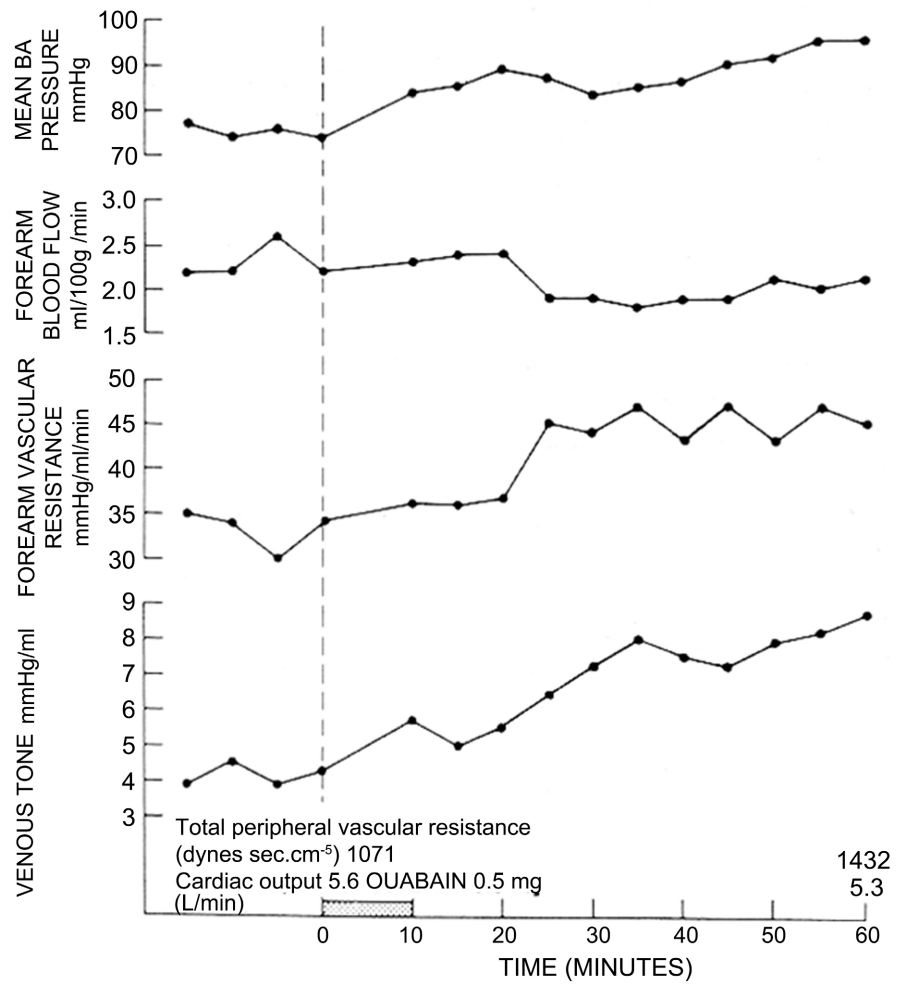


Figure 5. Digitalis in peripheral effect in patients without HF.

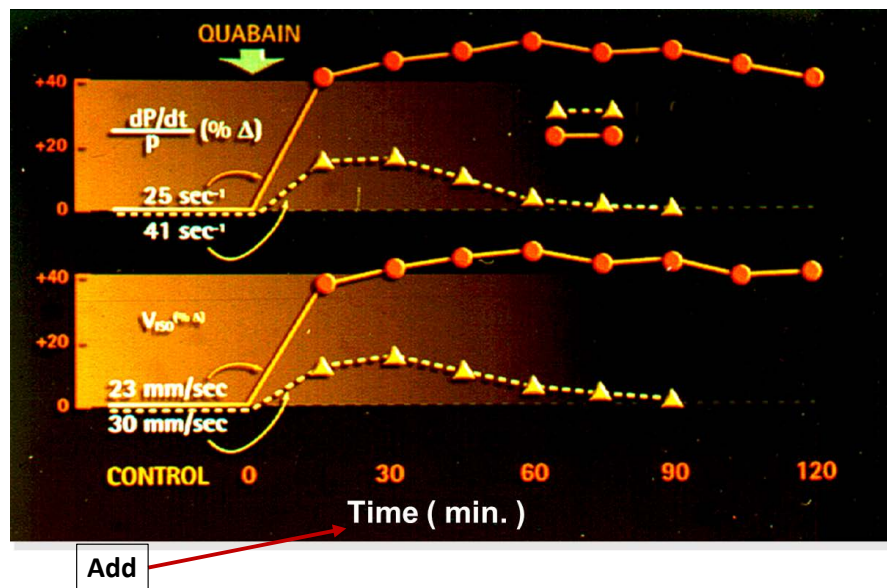


Figure 6. Effect of ouabain on dP/dT in normal and failing hearts in dogs with and without HF.

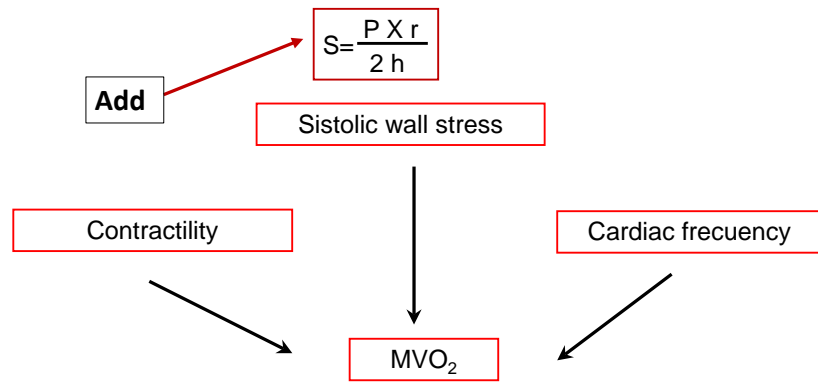


Figure 7. Determinants of myocardial oxygen consumption (MVO₂).

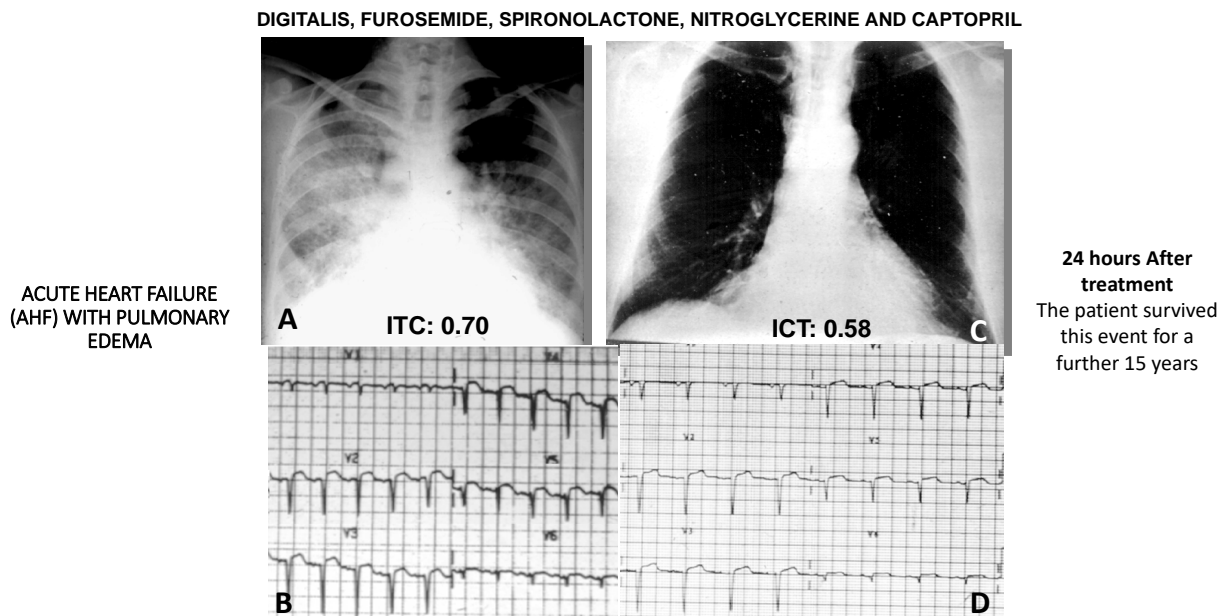
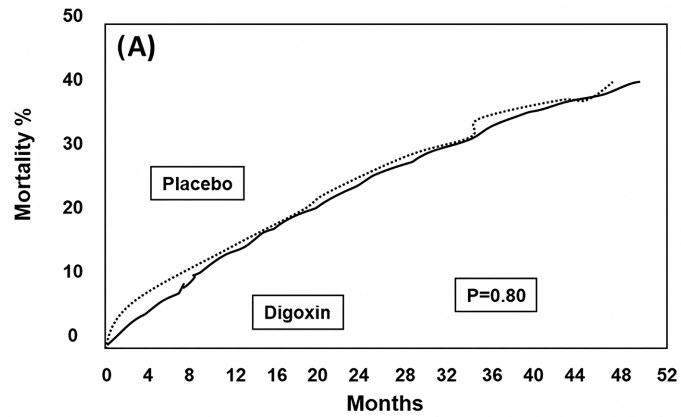


Figure 8. Digitalis in acute heart failure (pulmonary edema) in acute myocardial infarction.

nitroglycerin and captopril are administered, **Figure 8(C)** shows reduction of cardiomegaly with clear lung fields with asymptomatic patient 24 hours. After starting the treatment, in **Figure 8(D)** the ECG shows a HR of 98 × min, and the image of the infarction in progress.

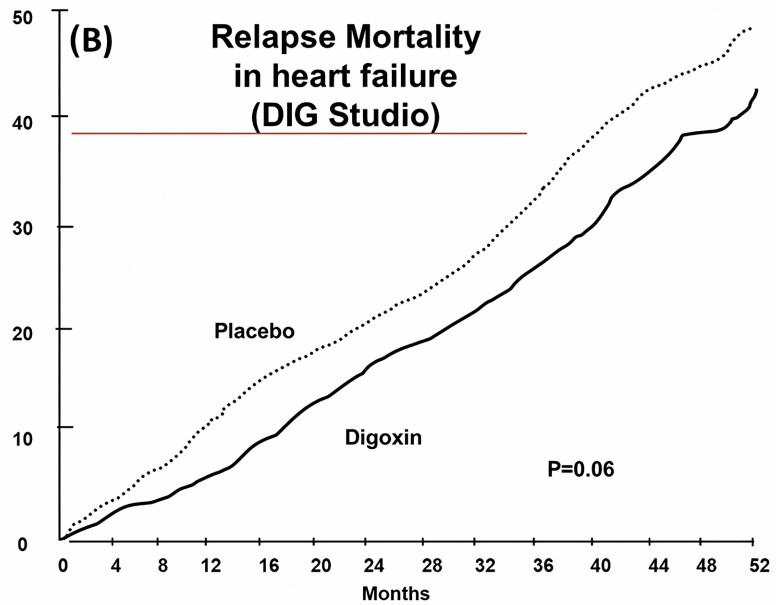
4. The First Scientific Study and Its of Digitalis Treatment Effect on Mortality

In 1997, the DIG study was carried out in 8000 patients, in digitalis treatment and the results revealed that the pharmacological treatment did not make any difference with placebo (**Figure 9(A)**) [8], the reduction of mortality only occurred when relapses (**Figure 9(B)**). After this study, the use of digitalis medication has declined to such an extent that clinical guidelines only use it when heart failure is complicated by atrial fibrillation, which is a very minor indication.



Placebo	3403	3239	3105	2976	2868	2758	2652	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Charge these images



Placebo	3403	3239	3105	2976	2868	2758	2656	2551	2205	1881	1506	1168	734	339
Digoxin	3397	3269	3144	3019	2882	2759	2644	2531	2184	1840	1475	1156	737	335

Figure 9. Effect of digitalis on mortality in chronic heart failure.

We proposed to carefully review the DIG study regarding the effects of digitalis medication in heart failure and when looking at the DIG [8] study of 8000 (Figure 9(A)) HF patients, the question arises, why were 1000 patients who had minimally depressed EF > 45% (Figure 10) or no HF. When previous studies had already shown that digitalis had no effect, which obviously contaminates the mortality statistics when 1000 patients have no or minimal HF, since there is evidence which shows that the mortality of this disease is directly proportional to the reduction in the EF [9] [10] [11] [12].

5. The DIG Sub-Study in Relation to Mortality

When the evidence of the effects of digitalis medication is analyzed, the great

value of the recently published article by Gheorghiade *et al.* [13] can be understood in which he rescues the true value of digitalis medication when he ranks the most severe patients in the DIG [8] study: in **NYHA functional class III - IV**, with **EF < 25%** and **WHR > 55%** and demonstrates that the mortality of this group of patients with the highest risk at 37.9 months (Figure 10), even, Gheorghiade and Braunwald [14] suggest that digitalis should be used in patients with acute severe heart failure, fact that we have corroborated in clinical practice (Figure 11).

6. Others Studies on Prevention of Digitalis in Relapses in Heart Failure

The studies PROVED and RADIANCE TRIAL (Figure 12) showed that in patients who were hospitalized for symptomatic HF who were discharged asymptomatic, a group with only diuretic and placebo, 44% returned to the hospital at 3 months, with symptomatic HF; another group was discharged with ACEI, diuretic and placebo and at 3 months, 30% returned with relapsed in HF; other

Ancillary Trial (Left Ventricular Ejection Fraction, >0.45)

In the ancillary trial, there were no significant differences in base-line characteristics between the 492 patients assigned to digoxin and the 496 patients assigned to placebo. There were 115 deaths in the digoxin group (23.4 percent) and 116 deaths in the placebo group (23.4 percent; risk ratio, 0.99; 95 percent confidence interval, 0.76 to 1.28). With regard to the combined outcome of death or hospitalization due to worsening heart failure, the results in

delete this text in yellow color

Figure 10. 1000 patients with normal or slightly decreased EF (DIG).

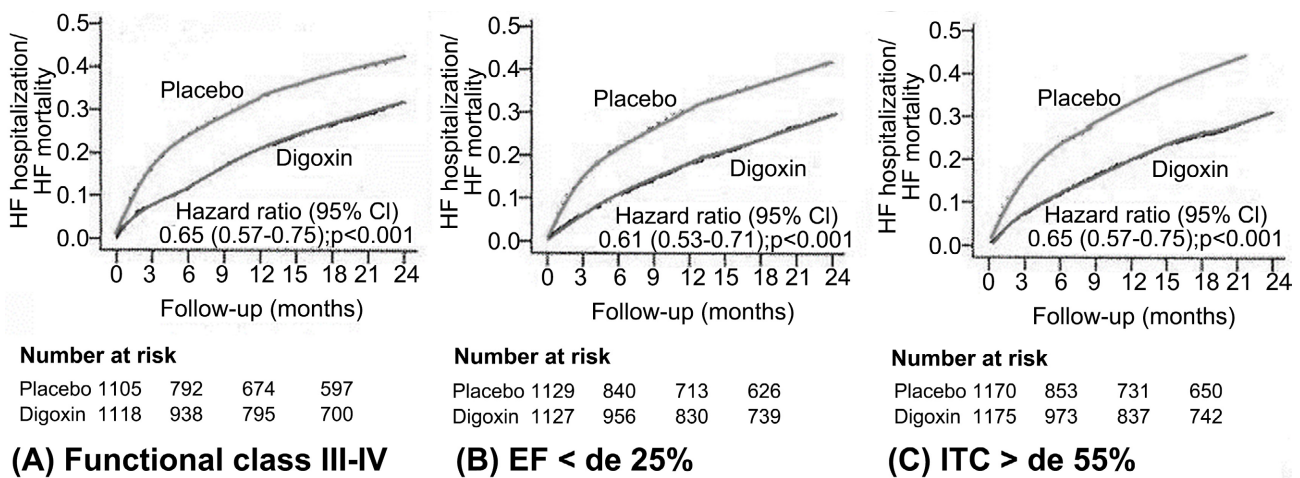


Figure 11. DIG sub-study. Mortality in the most severe patients.

group were discharged with digoxin, diuretics and placebo, the relapse was 20% and finally, when they were discharged with the triple regimen, only 5% of the patients relapsed, which shows that the combined therapy is superior to isolated treatment.

7. Other Beneficial Pharmacological Effects of Digitalis in HF

Digitalis has a modulating effect on the neuroendocrine system, by blocking the catecholamines and renin secretion in patients with symptomatic HF [15] [16] (Figure 13).

By other hand its vagal effect, restores the function of the baroreceptors (Figure 14) with heart rate variability is recovered in these patients [16] [17] which, as we know, reduces the possibility of sudden death, finally, digitalis, due to its vagal effect by reducing heart rate, restores the Bowditch effect (Figure 15), which is lost with sinus tachycardia sustained by adrenergic activation [18] [19].

The results of Gheorghiad study is similar to COPERNICUS Study (Figure 16)

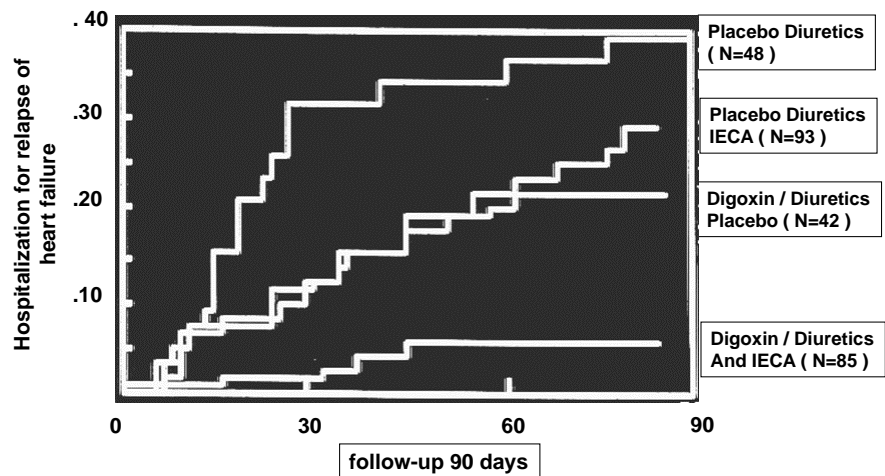


Figure 12. Digitalis in heart failure.

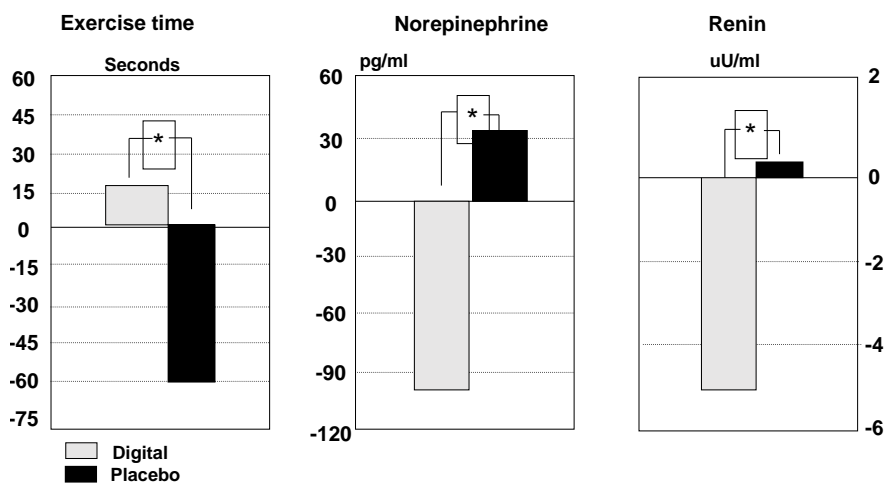


Figure 13. Digitalis effect of neuroendocrine system.

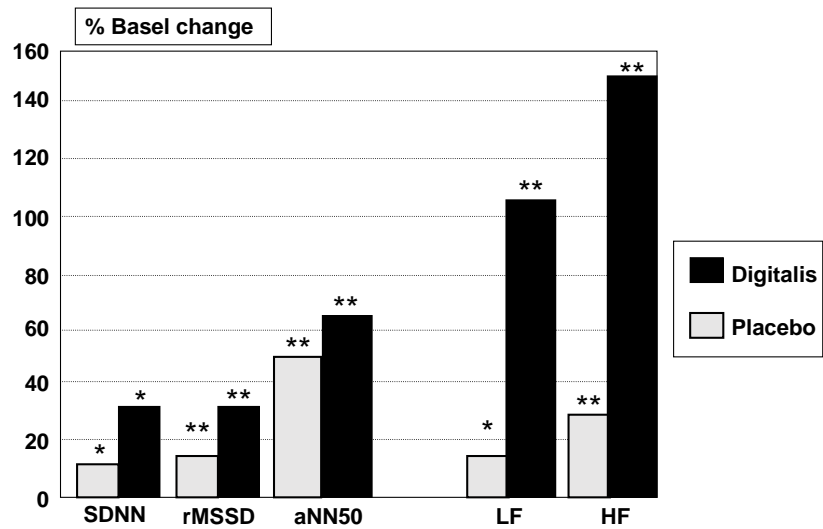


Figure 14. Digitalis effect on heart rate variability.

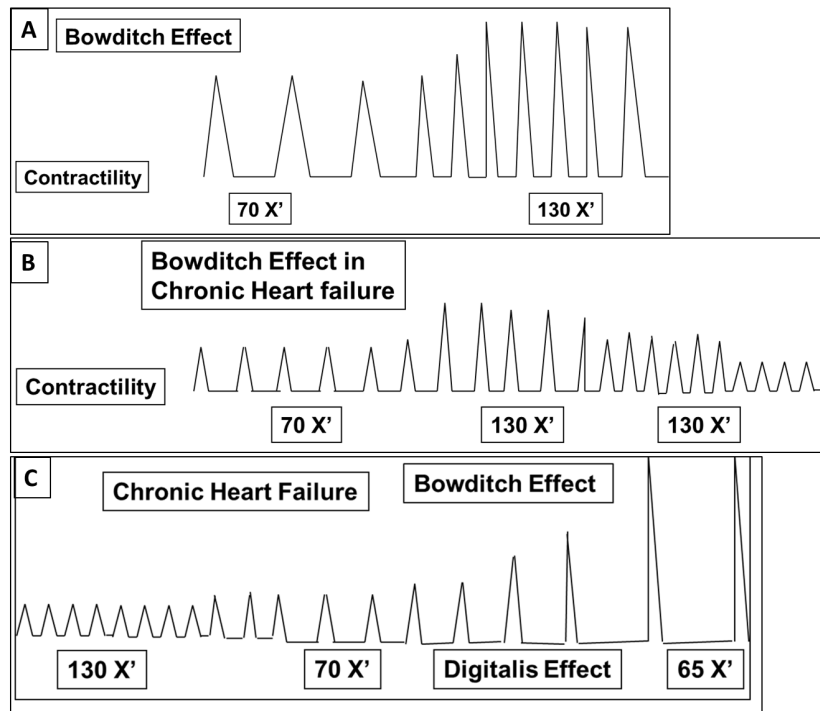


Figure 15. (A) Bowditch effect: force/frequency relationship. Increased heart rate increases contractility. (B) Sustained tachycardia, on the other hand, reduces contractility. (C) Digitalis administration in chronic heart failure due to its vagal effect reduces tachycardia and increases contractility.

[20] in relation of mortality achieved by Carvedilol in patients with HF in functional class IV.

Medications currently accepted for the treatment of HF: digitalis, diuretics, spironolactone, ACE inhibitors, beta-blockers, sacubitril-valsartan and gliflozina, have shown their maximum usefulness in combination by adding their pharmacological benefits; each one in isolation has a significantly lower beneficial

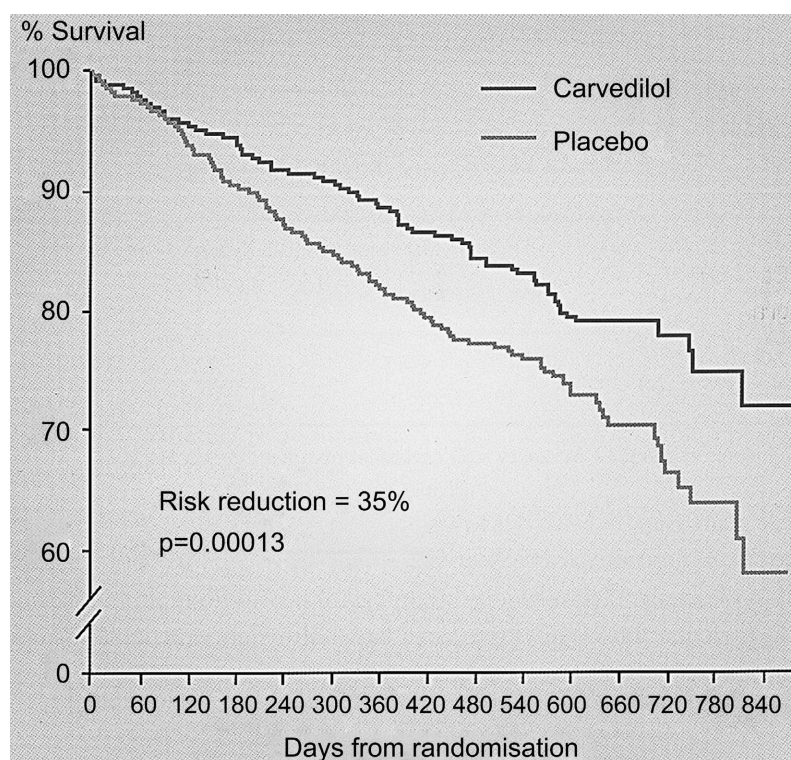


Figure 16. Carvedilol in heart failure in functional class IV (Copernicus study).

Table 1. Digitalis in heart failure.

CONCLUSIONS:

- 1) Digitalis is the ONLY inotropic drug that REDUCES MVO_2 in patients with heart failure, including patients with acute myocardial infarction.
- 2) Digitalis blocks the neuroendocrine system (catecholamines and renin), like IECA and betabloquers.
- 3) Restores baroreceptor function and heart rate variability.
- 4) Restores the Bowditch effect.
- 5) The combined therapy has better results and can be used in both acute and chronic heart failure.
- 6) Reduces in combined therapy mortality in patients with heart failure, especially in the most severe patients.

effect, but the combination between them, which must be individualized to the condition of each patient, improves functional class and reduces mortality, which is the most important objective in patients with HF.

8. Conclusion

The clinician and especially the cardiologist, thoroughly understands the digitalis effect in patients with and without heart failure, and all the pharmacological characteristics on inotropism, the neuroendocrine system, the autonomic nervous system, heart rate, baroreceptors, the Bowditch effect, functional class, beneficial effect on mortality reduction, the clinician will be able to make a correct use of the digitalis medication of its benefits, toxic effects, its contraindications

of patients with heart failure, in other words, the cardiologist must have a fine clinical skills for treatment to this patients (**Table 1**).

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

References

- [1] Guadalajara-Boo, J.F. (2022) Historia Gráfica de la Cardiología Mexicana en el siglo XX. Méndez Editores, Mexico City.
- [2] Chávez, I. (1920) La digitalina a pequeñas dosis, en el tratamiento de las cardiopatías. Tesis recepcional. Facultad de Medicina. Universidad Nacional Autónoma de México.
- [3] Braunwald, E., Goldberg, L.I. and Morrow, A.G. (1961) Studies on Digitalis. IV. Observations in Man on the Effects of Digitalis Preparations on the Contractility of the Non-Failing Heart and on Total Vascular Resistance. *Journal of Clinical Investigation*, **4**, 52-59. <https://doi.org/10.1172/JCI104236>
- [4] Mason, D.T. and Braunwald, E. (1964) Studies on Digitalis. X. Effects of Ouabain on Forearm Vascular Resistance and Venous Tone in Normal Subjects and in Patients in Heart Failure. *Journal of Clinical Investigation*, **43**, 532-538. <https://doi.org/10.1172/JCI104939>
- [5] Vatner, S.F. and Braunwald, E. (1974) Effects of Chronic Heart Failure on the Inotropic Response of the Right Ventricle of the Conscious Dog to a Cardiac Glycoside and to Tachycardia. *Circulation*, **50**, 728-734. <https://doi.org/10.1161/01.CIR.50.4.728>
- [6] Braunwald, E. (1971) Control of Myocardial Oxygen Consumption: Physiologic and Clinical Considerations. *The American Journal of Cardiology*, **27**, 416-432. [https://doi.org/10.1016/0002-9149\(71\)90439-5](https://doi.org/10.1016/0002-9149(71)90439-5)
- [7] Covell, J.W., Braunwald, E., Ross, I. and Sonnenblick, E.H. (1966) Studies on Digitalis. XVI Effects on Myocardial Oxygen Consumption. *Journal of Clinical Investigation*, **45**, 1535-1541. <https://doi.org/10.1172/JCI105460>
- [8] The Digitalis Investigation Group Investigators (1997) The Effects of Digoxin on Mortality and Morbidity in Patient Whit Heart Failure. *The New England Journal of Medicine*, **336**, 525-533. <https://doi.org/10.1056/NEJM199702203360801>
- [9] Volpi, A., De Vita, C., Franzosi, M.G., Geraci, E., Mauri, F., Negri, E., *et al.* (1993) Determinant of Six-Monts Mortality in Survivors of Myocardial Infarction Alter Thrombolysis Results of the GISSI-2 Database. *Circulation*, **88**, 416-429. <https://doi.org/10.1161/01.CIR.88.2.416>
- [10] Curtis, J.P., Sokil, S.I., Wang, Y., Rathore, S.S., Ka, D.T. and Jadbaba, F. (2003) The Association of Left Ventricular Ejection Fraction Mortality as Cause of Death in Stable out Patients with Heart Failure. *Journal of the American College of Cardiology*, **42**, 736-742. [https://doi.org/10.1016/S0735-1097\(03\)00789-7](https://doi.org/10.1016/S0735-1097(03)00789-7)
- [11] Aronow, W.S., Ahn, C. and Kronson, I. (1990) Prognosis of Congestive Heart Failure in Elderly Patient in Normal vs Abnormal Left Ventricular Systolic Function Associated with Coronary Artery Disease. *The American Journal of Cardiology*, **66**, 1257-1259. [https://doi.org/10.1016/0002-9149\(90\)91112-J](https://doi.org/10.1016/0002-9149(90)91112-J)
- [12] Cohn, J.N. and Rector, T.S. (1988) Prognosis of Congestive Heart Failure and Pre-

- dictors on Mortality. *The American Journal of Cardiology*, **62**, 25A-30A.
[https://doi.org/10.1016/S0002-9149\(88\)80081-X](https://doi.org/10.1016/S0002-9149(88)80081-X)
- [13] Gheorghide, M., Patel, K., Filippatos, N.G., Anker, S.D., Van Veldhuisen, D.J., Cleland, J.G.F., *et al.* (2013) Effect of Oral Digoxin in High-Risk Heart Failure Patients: A Pre-Specified Subgroup Analysis of the DIG Trial. *European Journal of Heart Failure*, **15**, 551-559. <https://doi.org/10.1093/eurjhf/hft010>
- [14] Gheorghide, M. and Braumwald, E. (2009) Recopnsidering the Role for Digoxin in the Management of Acure Heart Failure Síndromes. *JAMA*, **302**, 2146-2147.
<https://doi.org/10.1001/jama.2009.1657>
- [15] Tauke, J., Goldstein, S. and Gheorghide, M. (1994) Digoxin in Chronic Heart Failure: A Review of Randomized Controlled Trials with Special Attention to the Proved and Radiance Trial. *Progress in Cardiovascular Diseases*, **37**, 49-58.
[https://doi.org/10.1016/S0033-0620\(05\)80051-9](https://doi.org/10.1016/S0033-0620(05)80051-9)
- [16] Gheorghide, M. and Ferguson, D. (1991) Digoxin. A Neurohormonal Modulator in Heart Failure. *Circulation*, **84**, 2181-2186.
<https://doi.org/10.1161/01.CIR.84.5.2181>
- [17] Ferrari, A., Gregorini, L., Ferrari, M.C., Preti, L. and Mancía, G. (1981) Digitalis and Baroreceptor Reflexes in Man. *Circulation*, **63**, 279-285.
<https://doi.org/10.1161/01.CIR.63.2.279>
- [18] Mahler, F., Yoran, C. and Ross Jr., J. (1974) Inotropic Effect of Tachycardia and Post Stimulation Potentation in Conscious Dog. *American Journal of Physiology-Legacy Content*, **227**, 569-575. <https://doi.org/10.1152/ajplegacy.1974.227.3.569>
- [19] Hasenfuss, G., Holubarsch, C., Herman, H.P., Pieske, A.B. and Just, H. (1994) Influence of the Force-Frecuency Relationship on Hemodinamics and Left Ventricular Function in Patients with Non-Failure Hearts and in Patients with Dilated Cardiomyopathy. *European Heart Journal*, **15**, 164-170.
<https://doi.org/10.1093/oxfordjournals.eurheartj.a060471>
- [20] Packer, M., Fowler, M.B., Roecker, E.B., Coats, A.J.S., Katus, H.A. and Krum, H. (2002) Effect of Carvedilol on the Morbidity of Patients with Severe Chronic Heart Failure. Results of the Carvedilol Prospective Randomized Cumulative Survival (COPERNICUS) Study. *Circulation*, **106**, 2194-2199.
<https://doi.org/10.1161/01.CIR.0000035653.72855.BF>