



**HAL**  
open science

## Ouabain - The Insulin of the Heart

Hauke Fürstenwerth

► **To cite this version:**

Hauke Fürstenwerth. Ouabain - The Insulin of the Heart. *International Journal of Clinical Practice*, 2010, 64 (12), pp.1591. 10.1111/j.1742-1241.2010.02395.x. hal-00599542

**HAL Id: hal-00599542**

**<https://hal.science/hal-00599542v1>**

Submitted on 10 Jun 2011

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



**Ouabain – The Insulin of the Heart**

Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-12-09-0760.R1
Manuscript Type:	Perspective
Date Submitted by the Author:	18-Jan-2010
Complete List of Authors:	Fürstenwerth, Hauke; Hauke Fürstenwerth, consultant
Specialty area:	



1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

Title: **Ouabain – The Insulin of the Heart**

Author: Dr. Hauke Fürstenwerth  
Unterölbach 3A  
D-51381 Leverkusen  
Germany  
Phone: +49-2171-733740  
e-mail: [hauke@fuerstenwerth.com](mailto:hauke@fuerstenwerth.com)

corresponding author: Dr. Hauke Fürstenwerth  
Unterölbach 3A  
D-51381 Leverkusen  
Germany  
Phone: +49-2171-733740  
e-mail: [hauke@fuerstenwerth.com](mailto:hauke@fuerstenwerth.com)

disclosure: no conflict of interest

For Peer Review Only

**Abstract:**

Prior to the introduction of modern drugs like angiotensin converting enzyme inhibitors and  $\beta$ -adrenergic receptor antagonists, the cardiac glycoside ouabain (referred to as g-Strophanthin in German) has routinely been used in treatment of heart diseases. Decades of practical use indicate benefits in prevention and treatment of acute heart attacks. Prophylactic and therapeutic use of ouabain was recommended in insufficiencies of the left ventricle. This clinical experience disappeared in time, yet there is mounting evidence that supports a re-evaluation of ouabain in the treatment of heart disease. In 1991 ouabain was identified as an endogenous hormone. This discovery has lead to an intense re-examination of the drug, its physiological functions and its mode of action. New research illustrates the uniqueness of ouabain and thus confirms the extensive clinical experiences. Moreover, a recent study confirmed the long-known clinical observation that ouabain has an inhibitory effect on cardiotoxicity induced by other digitalis glycosides.

Deleted: is

Mechanistic studies have validated the clinical experience that ouabain is different from other cardiac glycosides. In contrast to digitalis glycosides ouabain modulates the metabolism of the heart; it stimulates substrate utilization of the myocardium, removes lactate accumulated during heart diseases, and reduces the amount of fatty acids in the blood. This profile makes ouabain a valuable prototype for new drugs, which offer new approaches for causal treatment of heart diseases. Clinical studies with ouabain that correspond to current standards are warranted.

**Review Criteria:**

An excessive literature research was performed on clinical experience with ouabain as well as on research on mode of action of ouabain and related cardiac steroids.

**Message for the clinic:**

Clinical experience suggests that ouabain has a favorable therapeutic profile in treatment of insufficiencies of the left ventricle. Ouabain modulates the metabolism of the heart. Clinical studies that correspond to current standards are warranted.

## Ouabain – The Insulin of the Heart

Today, medical therapies for heart disease are based on a diverse range of drugs. Angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists,  $\beta$ -adrenergic receptor antagonists, aldosterone receptor antagonists, as well as diuretics, and inotropic agents improve clinical symptoms and slow the progression of contractile dysfunction. Despite these therapeutic advances, heart failure is still associated with an annual mortality rate of 10% [1]. The search for better treatments and optimization of existing ones remain major challenges in cardiology.

Modulation of myocardial metabolism has become an accepted new approach to improve the performance of the dysfunctional myocardium [2]. Alternatively, proven agents such as digitalis glycosides continue to be of interest. Digoxin is still used extensively worldwide and it remains one of the most commonly prescribed drugs. The Digitalis Investigation Group trial has indicated that digoxin is quite effective in reducing cardiovascular hospitalizations [3]. A proposal for a large digoxin study is being considered for funding in Europe [4]. However, arrhythmia and a narrow therapeutic index limit its therapeutic application [5, 6].

Although often used as research tool, the cardiac glycoside ouabain (referred to as g-Strophanthin in German) has become a niche product in treatment of heart diseases. Decades of practical use indicate benefits in prevention and treatment of acute heart attacks. Prophylactic and therapeutic use of ouabain is recommended in insufficiencies of the left ventricle. Several clinical studies with orally administered ouabain report exceptionally positive results for treatment of cardiovascular diseases [7-9].

This clinical experience disappeared in time, yet there is mounting evidence that supports a re-evaluation of ouabain in the treatment of heart disease. In 1991 ouabain was identified as an endogenous hormone. This discovery has led to an intense re-examination of the drug, its physiological functions and its mode of action [10-12].

Based on its chemical structure ouabain is considered a typical digitalis derivative. All digitalis derivatives bind to and inhibit the ubiquitous transmembrane protein  $\text{Na}^+$ ,  $\text{K}^+$ -ATPase and increase the force of contraction of heart muscle. However, there are diverse biological responses to different derivatives both at the cellular and at the molecular level [13]. There are marked differences between the effects of digoxin and ouabain. Only ouabain in small doses stimulates the sodium pump [14, 15]; digoxin does not show this effect [16]. Moreover, digoxin was shown to induce changes in intracellular membrane traffic in neuronal cells, while ouabain does not possess this ability and even antagonized digoxin effect [17]. A recent study confirmed the long-known clinical experience that ouabain has an inhibitory effect on cardiotoxicity induced by digitalis glycosides. Ouabain at a low dosage delayed the start of arrhythmia induced by digoxin on guinea pig papillary muscle. In addition, ouabain at a low dosage but not at a high dosage delayed the development of digoxin-induced arrhythmia in anaesthetized guinea pigs [18]. Thus the long-known characteristic dose dependency of ouabain effects [21] has been confirmed.

Deleted: very

Deleted: , 11

Deleted: 2

Deleted: 3

Deleted: 4

Deleted: 5

Deleted: it was shown that ouabain inhibits digoxin-induced changes in membrane traffic

Deleted: 6

Deleted: 7

Deleted: 0

### Clinical Experience with Ouabain

According to canonical explanations, ouabain and other digitalis derivatives should have similar therapeutic effects. However, clinical experience clearly indicates that ouabain is different from other digitalis derivatives. A most pronounced difference is the fast onset of action by ouabain. This effect was the basis for the chance discovery of ouabain in 1859 by the English botanist Kirk. He had discovered the fast onset of action of ouabain on the heart by using a toothbrush contaminated with Strophanthus seeds. The rapid onset of effect of oral ouabain was used in medical practice for a "Strophanthin-quick-test": patients with suspected heart disease were given two tablets of 3 mg that they had to chew and distribute in the mouth. In the case of heart disease a relief of complaints was observed within 5-10 minutes. This test was used routinely in German physicians' offices well into the 1970s.

Based on decades of extensive clinical experience with ouabain the therapeutic profile of the drug and the disease profiles for which the use of ouabain is appropriate have been summarized in monographs and reviews [19-21]. The main benefit is in prevention and treatment of acute heart attacks. Prophylactic and therapeutic use of ouabain is recommended in: congestive heart insufficiency without pronounced hypertrophy, coronary sclerosis, cardiogenic hypertension, asthma cardiale, exercise-induced cardiac insufficiency, angina pectoris and arrhythmias, including those that occur on treatment with digitalis. It is stated that ouabain "has proven to be the most acceptable, most effective antidote for digitalis intoxication."

Edens described "the intravenous Strophanthin treatment as the safest treatment of organic-induced angina pectoris, including heart attack." Digitalis causes a worsening of symptoms and is therefore contra-indicated. While under digitalis ECG abnormalities and arrhythmias can occur, these symptoms are either alleviated or completely abolished by ouabain [22, 23]. In addition, there are numerous clinical reports that ouabain lowers blood pressure in patients with heart diseases [24, 25].

In the 1950s a fierce scientific dispute erupted over the bioavailability of orally administered ouabain. In the 1970s optimized enteric-coated formulations were introduced that have enteral absorption rates of up to 80% in cats [26]. A drug based on such a formulation today is registered for insufficiency of the left ventricle in Germany, sold as prescription drug under the brand name Strodival<sup>®</sup> mr by Medapharma. An investigation published in 2001 reports systemic bioavailability of 43 to 50% after oral administration in guinea pigs [27].

### Ouabain Modulates Cardiac Metabolism

Based on extensive clinical observations it had been postulated that ouabain stimulates myocardial metabolism [19-21]. Mechanistic studies have revealed that ouabain, in contrast to digitalis derivatives, indeed has pronounced effects on the cardiac metabolism. In dogs ouabain increases lactic acid utilization by the myocardium. Yet digitoxin inhibits lactic acid

Deleted: 8

Deleted: 0

Deleted: 1

Deleted: 2

Deleted: 3

Deleted: 4

Deleted: 5

Deleted: 6

Deleted: 8

Deleted: 0

utilization by the myocardium [28]. Ouabain as well as k-strophanthin reduce lactic acid concentration in the blood of patients with heart diseases [29, 30].

Deleted: 7

Deleted: 8

Deleted: 29

The metabolic effect of ouabain is not limited to stimulation of lactic acid utilization. Upon oral administration to male rats ouabain increases the acetyl-coenzyme A/coenzyme A ratio in the myocardium [31]. Contrary to digitoxin, ouabain stimulates fatty acid utilization in the myocardium [32, 33]. Ouabain amplifies metabolic stimulation induced by acetylcholine and inhibits increased oxygen consumption induced by adrenaline [34]. In the failing human myocardium the positive haemodynamic effects of ouabain are not associated with additional energy consumption [35]. In contrast, in healthy male subjects digoxin reduces resting metabolic rate, respiratory quotient and fat oxidation [36]. In an infarct model with the guinea pig heart, digoxin has no stimulating effects on cardiac metabolism [37]. The digitalis derivative Lanatoside-C has no effect on substrate utilization of the myocardium [38].

Deleted: 0

Deleted: 1

Deleted: 2

Deleted: 3

Deleted: 4

Deleted: 5

Deleted: 6

Deleted: 7

In addition to the effects on fatty acid metabolism, ouabain stimulates myocardial protein syntheses [39]. Digitoxin inhibits myocardial protein synthesis [31].

Deleted: 8

Deleted: 0

Manfred von Ardenne demonstrated that in myocardial infarction induced by ligature in rat and rabbit hearts the pH in myocardial tissue drops markedly. This acidification triggers a chain reaction that leads to cell death [40]. Administration of ouabain in a myocardial infarct model in rats raises the pH of acidic cardiac tissue within a few minutes by up to 0.5 units. Digitoxin does not alter the pH. In addition, ouabain increases the rheological properties of blood by enhancing the plasticity of erythrocytes [41]. Digitoxin does not influence the flexibility of erythrocytes.

Deleted: 39

Deleted: 0

The pH sensitivity of the myocardium is well documented. A drop in pH below 6.2 leads to irreversible damage. Therefore, in cardiac surgery strict pH control is imperative [42]. In the "Strophanthin era" German surgeons routinely applied 0.3 mg ouabain pre-operatively and thereby observed significantly fewer complications [43].

Deleted: 1

Deleted: 2

The metabolic effects of ouabain are supported by in vivo studies. Ouabain significantly increases the endurance performance of rats. Hypertrophy of the heart is reduced by administration of ouabain [44]. Orally administered ouabain improves physical endurance in guinea-pigs [45] as well as in healthy volunteers [46]. Digoxin, however, does not improve the performance of patients with coronary arterial disease. In a double-blind crossover study with k-strophanthin and digoxin only k-strophanthin improved the performance of coronary patients [47].

Deleted: 3

Deleted: 4

Deleted: 5

Deleted: 6

Additional evidence confirms the mechanistic differences between ouabain and digitalis glycosides. Ouabain and digitalis derivatives develop their effects in different cellular spaces. Digitalis derivatives must penetrate into the cell interior to exert their effects, whereas ouabain develops its effect in the extracellular space [48]. The pharmacokinetic behavior of iv-administered ouabain and digitalis derivatives likewise suggests that their therapeutic effects are based on different receptors. The effect of iv-administered ouabain starts immediately after injection, reaches a maximum after 5 minutes, last 5-7 hours and then

Deleted: 7

rapidly declines [22]. With iv-administered digoxin, effects slowly start 5-30 minutes after injection, the maximum effect being reached only after 1-4 hours [5].

Deleted: 1

### Conclusion

Research on ouabain has suffered from the dogma that ouabain is a member of the digitalis glycosides. Recent research illustrates the uniqueness of ouabain and confirms the clinical experiences with ouabain, which have been known for decades. Ouabain modulates the metabolism of the heart; it stimulates substrate utilization of the myocardium, removes lactate accumulated during heart diseases, and reduces the amount of fatty acids in the blood. Ouabain is, as Aschenbrenner has formulated, the insulin of the heart. The uniqueness of ouabain ought to be recognized in future research as well as in clinical practice. Clinical studies with ouabain that correspond to current standards are warranted.

### References

[1] Cleland JGF, Daubert J-C, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**:1539-49

Formatted: Font: Bold

[2] Neubauer S. The Failing Heart - An Engine Out of Fuel. *N Engl J Med* 2007;**356**:1140-1151

Deleted: ,

Deleted: ,

Formatted: Font: Bold

[3] Hauptman PJ and Kelly RA. Digitalis. *Circulation* 1999;**99**:1265-1270,

Formatted: Font: Bold

[4] Cleland JGF, Cullington D. Digoxin: Quo Vadis? *Circ Heart Fail* 2009;**2**: 81-85

Deleted: :

Formatted: Font: Bold

[5] Eichhorn EJ, Gheorghiade M, Digoxin. *Prog Cardiovasc Dis* 2002;**44**(4): 251-266

Formatted: Font: Bold

[6] Wasserstrom JA, Aistrup GL. Digitalis: new actions for an old drug. *Am J Physiol Heart Circ Physiol* 2005;**289**(5): H1781-1793

Deleted: ()

Formatted: Font: Bold

[7] Dohrmann RE, Dohrmann M. Neuere Therapie der instabilen Angina Pectoris bei Koronarer Herzkrankheit. *Erfahrungsheilkunde* 1984;**33**: 183-90

Deleted: :

Formatted: Font: Bold

[8] Dohrmann RE, Janisch HD, Kessel M. Klinisch-poliklinische Studie über die Wirksamkeit von g-Strophanthin bei Angina pectoris und Myokardinfarkt. *Cardiologisches Bulletin* 1977;**14/15**: 183-187

Deleted: :

Formatted: Font: Bold

[9] Halhuber M, Lantscherat T, Meusburger K. Zur Strophoraltherapie. *Med Klin* 1954;**36**:1440-1443

Deleted: :

Formatted: Font: Bold



[10] Bagrov AY, Shapiro JI, Fedorova OV, Endogenous Cardiotonic Steroids: Physiology, Pharmacology, and Novel Therapeutic Targets. *Pharmacol Rev* 2009; **61**: 9–38

Deleted: :

Formatted: Font: Bold

[11] Schoner W, Scheiner-Bobis G. Endogenous and exogenous cardiac glycosides: their roles in hypertension, salt metabolism, and cell growth: *Am J Physiol Cell Physiol* 2007; **293**: C509–C536

Formatted: Font: Bold

[12] Neshar M, Shpolansky U, Rosen H, Lichtstein D. The digitalis-like steroid hormones: new mechanisms of action and biological significance. *Life Sci.* 2007; **80**:2093-2107

[13] Dvela M, Rosen H, Feldmann T, et al. Diverse biological responses to different cardiotonic steroids: *Pathophysiology* 2007; **14**:159–166

Deleted: 2

Deleted: Neshar M, Lichtstein D,

Formatted: Font: Bold

[14] Oberfrank F, Vizi ES, Baker PF, et al. Comparison of the effects of a bufodienolide and ouabain on neuronal and smooth muscle preparations: *Neurosci. Res.* 1991; **10**:235–244.

Deleted: 3

Deleted: Samuelov S, Lichtstein D,

Formatted: Font: Bold

[15] Gao J, Wymore RS, Wang Y, et al. Isoform-specific stimulation of cardiac Na/K pumps by nanomolar concentrations of glycosides: *J. Gen. Physiol.* 2002; **119**:297–312.

Deleted: 4

Deleted: Gaudette GR, Krukenkamp IB, Cohen IS, Mathias RT,

Formatted: Font: Bold

[16] Balzan S, D'Urso G, Ghione S, et al. Selective inhibition of human erythrocyte Na<sup>+</sup>/K<sup>+</sup> ATPase by cardiac glycosides and by a mammalian digitalis like factor: *Life Sci.* 2000; **67**:1921–1928.

Deleted: 5

Deleted: Martinelli A, Montali U,

Formatted: Font: Bold

[17] Feldmann, T, Glukmann, V, Medvenev, et al. Role of endosomal Na<sup>+</sup>-K<sup>+</sup>-ATPase and cardiac steroids in the regulation of endocytosis. *American Journal of Physiology. Cell Physiology* 2007; **293**(3): C885-896

Deleted: 6

Deleted: E, Shpolansky, U, Galili, D, Lichtstein, D, Rosen, H (2007)

Deleted: 7

[18] Neshar M, Shpolansky U, Viola N, et al. Ouabain attenuates other cardiac steroid-induced cardiotoxicity: *Br J Pharmacol*, 2010, *in press*

Deleted: Dvela M, Buzaglo N, Cohen Ben-Ami H, Rosen H, Lichtstein D,

Formatted: Font: Bold

[19] Edens E, *Die Digitalisbehandlung*. 3. Auflage, Verlag Urban&Schwarzenberg, Berlin-München; 1948

Deleted: 8

[20] Kern B, *Der Myokardinfarkt*. 3. Auflage, Haug Verlag, Heidelberg; 1974

Deleted: :

Deleted: 19

[21] Zimmermann H, Die klinische Strophanthinlehre von Edens im Lichte neuer Forschungsergebnisse, *Med Klin* 1951; **46**: part I: 1028-1031, part II: 1049-1052,

Deleted: :

Deleted: 0

Deleted: H.

[22] Sarre H, Die Ursache der gegensätzlichen Wirkung von Strophanthin und Digitalis auf die Coronarinsuffizienz: *Klin Wochenschr* 1943; **22**:135

Deleted: ,

Formatted: Font: Bold

Deleted: 1

Deleted: :

Formatted: Font: Bold

- [23] Kubicek F, Reisner T. Hypoxietoleranz bei koronarer Herzkrankheit unter der Einwirkung von Digoxin, Beta-Methyl-Digoxin und g-Strophanthin. *Ther Ggw* 1973;**112**:747
- [24] Rothmund W. Über die Entstehung der essentiellen Hypertonie. *notabene medici* 1977;**7**:22-32
- [25] Kracke R. Zur perlingualen Strophanthintherapie. *Dtsch Med Wochenschr* 1954;79-81
- [26] United States Patent 4,202,888, filed on July 7, 1977 by Kali-Chemie Pharma GmbH
- [27] Leuschner J, Winkler A. Toxicological studies with ouabain. *Naunyn Schmiedebergs Arch Pharmacol.* 2001;**363 (4) Suppl.**:139, abstract 544
- [28] von Blumencron W. Über die Wirkung von Strophanthin und Digitoxin auf den Milchsäurestoffwechsel des Herzens. *Klin Wochenschr* 1941:737-739
- [29] Renk H. Vergleichende Untersuchungen über das Verhalten des Milchsäurespiegels bei der Therapie der Herzinsuffizienz. *Med Klin* 1959:13-16
- [30] Loll H, Blumenberger KJ. Änderungen des Serumspiegels von Intermediärprodukten und Enzymen durch k-Strophanthin. *Arztl Forsch* 1960:181-185
- [31] Kaemmerer K, Kietzmann M. Intermediäre Effekte von g-Strophanthin und Digitoxin im Tierversuch. *Cardiologisch-angiologisches Bulletin* 1987;**24**:66-70
- [32] Riehle M, Bereiter-Hahn J. Ouabain and Digitoxin as modulators of chick embryo cardiomyocyte energy metabolism. *Arzneimittelforschung* 1994;**44(8)**:943-947
- [33] Gousios AG, Felts JM. Effects of Ouabain on Force of Contraction, Oxygen Consumption, and Metabolism of Free Fatty Acids in the Perfused Rabbit Heart. *Circ Res* 1967;**21**:445-448
- [34] Gremels H. Über den Einfluß von Digitalisglykosiden auf die energetischen Vorgänge am Säugetierherzen. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 1937;**186**:625
- [35] Hasenfuss G, Mulieri LA, Allen PD, et al. Influence of isoproterenol and ouabain on excitation-contraction coupling, cross-bridge function and energetics in failing human myocardium. *Circulation* 1996;**94**: 3155-3160
- [36] Lyon X, Schutz Y, Buclin T, et. al. Inhibition of Na(+)-K(+) ATPase by digoxin and its relation with energy expenditure and nutrient oxidation rate. *Am J Physiol Endocrinol Metab* 1995;**268**: E1051-E1056

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

[37] Zannad F, Graham CW, Aronson JK. The effects of digoxin and dopamine on the oxygen consumption, lactate production and haemodynamic performance of an isolated, perfused, working guinea-pig heart: *Eur J Pharmacol.* 1982; **81(2)**: 263-71.

Deleted: 6

Formatted: Font: Bold

[38] Blain JM, Eddleman EE, Siegel A, Bing RJ. Studies on myocardial metabolism: V. Effects of lanatoside-C on the metabolism of the human heart: *J. Clin. Invest.* 1956; **35**: 314,

Deleted: 7

Deleted: .

Deleted: .

Deleted: .

Deleted: .

Formatted: Font: Bold

Deleted: 8

Deleted: :

Formatted: Font: Bold

[40] von Ardenne M. Research on the mechanism of myocardial infarctions and on counteracting measures, a new galenic form of the fast acting g-strophanthin. *Agressologie* 1978; **19**:13-22

Deleted: 39

Deleted: :

Formatted: Font: Bold

[41] Saradeth T, Ernst E. Hämorheologische Effekte durch g-Strophanthin. *Erfahrungsheilkunde* 1991; **40**:775-776

Deleted: 0

Deleted: :

Formatted: Font: Bold

[42] Healey CM, Kumbhani DJ, Healey NA, et al. Impact of intraoperative myocardial tissue acidosis on postoperative adverse outcomes and cost of care for patients undergoing prolonged aortic clamping during cardiopulmonary bypass: *Am J Surg.* 2009; **197(2)**: 203 – 10

Deleted: 1

Deleted: Crittenden MD, Gibson SF, Khuri SF

Formatted: Font: Bold

Deleted: :

[43] Kern B. *Strophanthin-Report*, page 43, edited by W. Mauss, Studienkreis für Infarktprobleme, Stuttgart, 1984

Deleted: 2

Deleted: Berthold

Deleted: .

[44] Kuschinsky G. Die Verhütung von Erschöpfungszuständen des Herzens durch Digitalissubstanzen. *Klin Wochenschr* 1947:502-503

Deleted: 3

Deleted: :

[45] Moskopf E, Dietz H. Experimentelle und klinische Untersuchungen über eine zuverlässige orale Strophanthintherapie. *Med Welt* 1955:1375-1377

Deleted: 4

Deleted: :

[46] Saradeth T, Ernst E. Hämorheologische Effekte durch g-Strophanthin. *Erfahrungsheilkunde* 1991; **40**:775-776

Deleted: 5

Deleted: :

Formatted: Font: Bold

[47] Agostoni PG, Doria E, Berti M, et. al. Better efficacy of K-strophanthin versus digoxin in subjects with dilated cardiomyopathy and chronic heart insufficiency. *Cardiologia* 1992; **37(5)**: 323-329

Deleted: 6

Deleted: :

Formatted: Font: Bold

Deleted: :

[48] Löhr E, Makoski HB, Göbbeler T, et. al. Beitrag zur Membranpermeabilität von Cardiaca (g-Strophanthin, Digoxin und Oxyfedrin) auf Grund von Mikro-Autotadiographien am Meerschweinchenherzen. *Arzneimittelforschung* 1971; **21**: 566

Deleted: :

Deleted: 7

Deleted: :

Formatted: Font: Bold