Israel Medical Journal, Vol. XXII, No. 11—12, 1963

CONTRACTILITY OF ISOLATED HEARTS FROM MYXEDEMATOUS RATS

F.L. MEIJLER, M.D.*

University Department of Cardiology, Amsterdam, and University Department of Clinical Endocrinology and Diseases of Metabolism, Leiden, The Netherlands

HYPOTHYROIDISM is often complicated by coronary sclerosis and cardiac failure[1]. It is generally believed that the coronary sclerosis is mainly caused by the disturbed lipoid metabolism[2]. The cardiac failure, however, is less well understood. Five explanations for cardiac insufficiency, if present in hypothyroid patients, can easily be found:

A. Evidence has been presented[3,4] that the rate of hearts contracting in vitro depends among others on the thyroid function of the animal from which those hearts were derived. These experiments suggest a direct effect of the thyroid hormone on the myocardium.

B. The hypometabolism of the body as a whole causes a decreased peripheral blood flow which results in a diminished venous return, possibly causing an insufficient cardiac output[5]. According to this view, the hypofunction of the heart is not located in the myocardium itself, but in the hypometabolism of the organism.

C. In some papers[6,7] a diminished catecholamine content of myocardium derived from hypothyroid animals is mentioned. Whalen[8] and Gaffney[9] produced evidence that the performance of the heart is related to its catecholamine content. Therefore it can be thought possible that the hypofunction of a myxedematous heart is due to a diminished amount of catecholamines.

D. The fourth explanation for the hypofunction of the hypothyroid heart can be found by considering its anatomical changes; "Das myxoedeem Herz"[10].

E. If in myxedema patients a severe coronary insufficiency exists, this may, at least in part, also impede the cardiac function. McBrien and Hindle[11] went so far that they claim that heart failure, if present, in myxedema patients is only due to coronary sclerosis and they deny an effect of hypothyroidism of itself.

Studying the contractility of isolated perfused hearts derived from hypothyroid rats, we have tried to elucidate the alternatives mentioned above. Under these experimental conditions the heart contractions are not influenced by venous return (A)[12]; the effect of thyroid hormone on the heart applicated in vitro or in vivo can easily be studied (B). After the experiments the catecholamine content

* With technical assistance of Mr. P. Brekelmans and Mr. W. Zuidervaart.

Israel Medical Journal, Vol. XXII, No. 11—12, 1963

CONTRACTILITY OF ISOLATED HEARTS FROM MYXEDEMATOUS RATS

F.L. MEIJLER, M.D.*

University Department of Cardiology, Amsterdam, and University Department of Clinical Endocrinology and Diseases of Metabolism, Leiden, The Netherlands

HYPOTHYROIDISM is often complicated by coronary sclerosis and cardiac failure[1]. It is generally believed that the coronary sclerosis is mainly caused by the disturbed lipoid metabolism[2]. The cardiac failure, however, is less well understood. Five explanations for cardiac insufficiency, if present in hypothyroid patients, can easily be found:

A. Evidence has been presented[3,4] that the rate of hearts contracting in vitro depends among others on the thyroid function of the animal from which those hearts were derived. These experiments suggest a direct effect of the thyroid hormone on the myocardium.

B. The hypometabolism of the body as a whole causes a decreased peripheral blood flow which results in a diminished venous return, possibly causing an insufficient cardiac output[5]. According to this view, the hypofunction of the heart is not located in the myocardium itself, but in the hypometabolism of the organism.

C. In some papers[6,7] a diminished catecholamine content of myocardium derived from hypothyroid animals is mentioned. Whalen[8] and Gaffney[9] produced evidence that the performance of the heart is related to its catecholamine content. Therefore it can be thought possible that the hypofunction of a myxedematous heart is due to a diminished amount of catecholamines.

D. The fourth explanation for the hypofunction of the hypothyroid heart can be found by considering its anatomical changes; "Das myxoedeem Herz"[10].

E. If in myxedema patients a severe coronary insufficiency exists, this may, at least in part, also impede the cardiac function. McBrien and Hindle[11] went so far that they claim that heart failure, if present, in myxedema patients is only due to coronary sclerosis and they deny an effect of hypothyroidism of itself.

Studying the contractility of isolated perfused hearts derived from hypothyroid rats, we have tried to elucidate the alternatives mentioned above. Under these experimental conditions the heart contractions are not influenced by venous return (A)[12]; the effect of thyroid hormone on the heart applicated in vitro or in vivo can easily be studied (B). After the experiments the catecholamine content

---

* With technical assistance of Mr. P. Brekelmans and Mr. W. Zuidervaart.

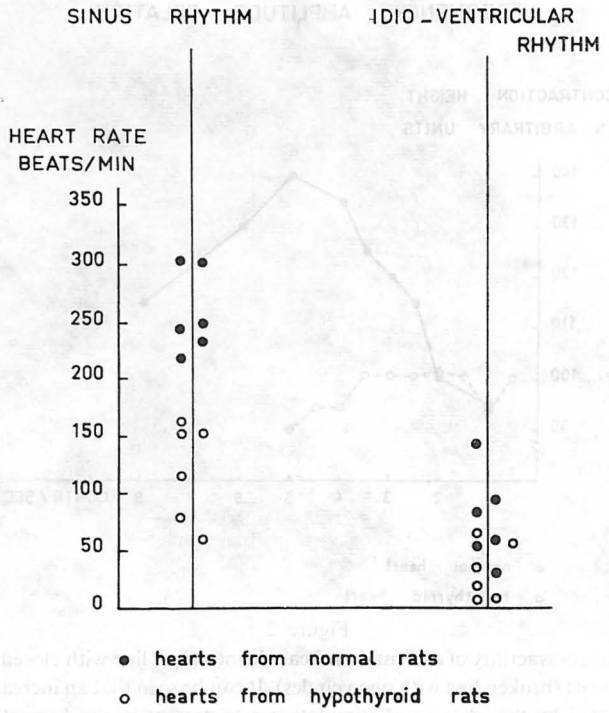

Figure 1

Comparison of the rate of the sinus rhythm and that of the idio-ventricular rhythm of normal rat hearts (closed circles) and of hypothyroid rat hearts (open circles). The difference in rate in both groups is evident.

present in normal hearts could not be demonstrated in hypothyroid hearts. This is shown in Fig. 2 derived from a representative experiment. It has already been said, that in isolated mammalian hearts perfused according to Langendorff mechanisms such as increased diastolic filling or increased diastolic lengthening of the myocardial fibers cannot be operative[12]. So that under these experimental conditions the decrease of the contractility of the hypothyroid hearts is probably caused by the lack of circulating thyroid hormone in the living animal.

We therefore tried to restore the contractility of these hearts by adding T3 or Triac to the perfusion fluid. In Fig. 3 is demonstrated that the contractility cannot be restored to normal by adding 20μg T3 to 1 liter of perfusion fluid. Attempts to get an in vitro effect of T3 by increasing the duration of the perfusion up to 6 hours or by adding albumin to the perfusion fluid also failed.

Knowing that adding T3 or Triac to the perfusion fluid remained without any effect on rate and the contraction mechanism we studied the influence of administering T3 to the intact animal. It was found that 3 $\times$ 5μg T3 injected intra-

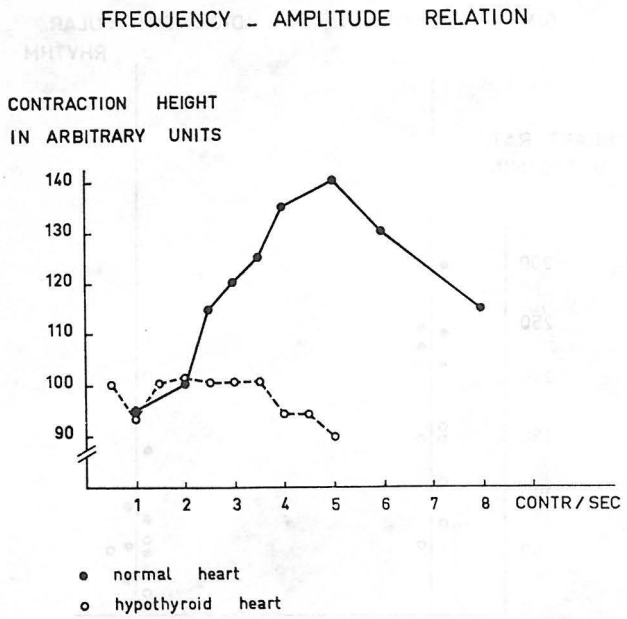

Figure 2

Relation of rate to contractility of a normal rat heart (continuous line with closed circles) and of a hypothyroid rat heart (broken line with open circles). It can be seen that an increase in contraction amplitude originated by the increase of stimulation rate present in the normal heart is lacking in the heart of the hypothyroid rat.

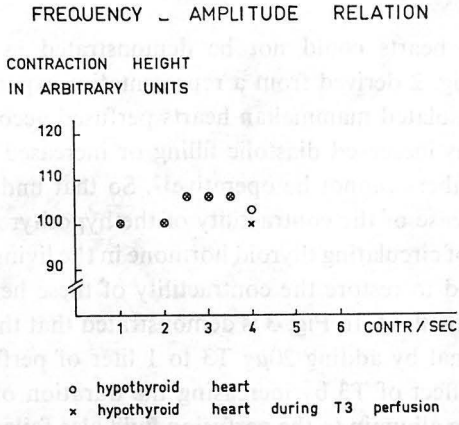

Figure 3

Relation of rate to contractility of a heart derived from a hypothyroid rat during perfusion without (open circles) and with (cross-marks) the addition of 20μ g triiodothyronine (T3) to the perfusion fluid. An effect of T3 cannot be demonstrated.

peritoneally on respectively 18, 12 and 6 hours before the experiment almost normalized the spontaneous frequency and the relation of frequency to contractility.

The latter is demonstrated in Fig. 4. The injecting of 1 × or 2 × 5 μg T3 had intermediate effects.

If in normal hearts a high stimulation rate is suddenly altered into a lower frequency, the amplitude of the first contractions of the lower frequency is in-

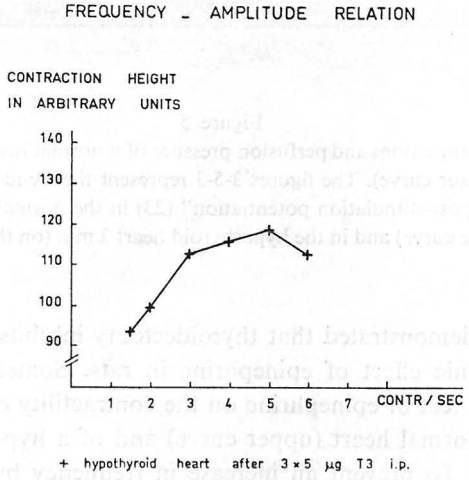

Figure 4

Relation of rate to contractility of a heart derived from a hypothyroid rat. Respectively on 6, 12 and 18 hours before the experiment 5 μg triiodothyronine was injected intraperitoneally. The relation of rate to contractility has almost been restored to normal. This diagram should be compared with those in Fig. 2 and 3.

creased in comparison to the amplitude of the contractions of the foregoing higher frequency. This is another aspect of the relationship between rhythm and contractility and is called "post-stimulation potentiation"[23]. This potentiation phenomenon has quantitatively highly been diminished in hearts derived from hypothyroid hearts. This is demonstrated in Fig. 5. The upper curve shows the contraction pattern of a normal heart, the lower curve that of a hypothyroid heart. In the normal heart the increase in contraction height originated by the high frequency period amounts to 5 mm (on the curve) while in the hypothyroid heart this is less than 2 mm. These values were found by substracting the amplitude of one beat of the first low frequency period (thus preceding the high frequency) from the amplitude of the first contraction of the second low frequency period (following the high frequency).

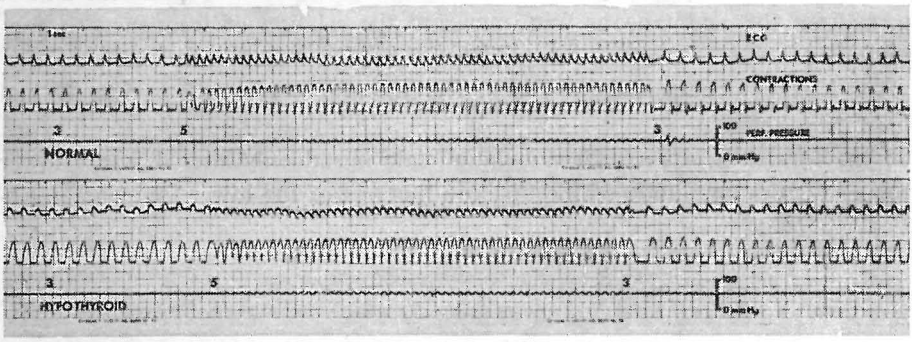

Figure 5

Electrocardiogram, contractions and perfusion pressure of a normal heart (upper curve) and of a hypothyroid heart (lower curve). The figures 3-5-3 represent the frequency in contractions/sec., thus 3/sec. etc. The "post-stimulation potentiation" (23) in the normal heart amounts to 5 mm (on the curve) and in the hypothyroid heart 2 mm (on the curve).

Swanson[24] has demonstrated that thyroidectomy inhibits and thyroxin potentiates the calorigenic effect of epinephrine in rats. Something analogue could be found for the effect of epinephrine on the contractility of the heart. In Fig. 6 the records of a normal heart (upper curve) and of a hypothyroid heart (lower curve) are shown. To prevent an increase in frequency by the epinephrine the effect of epinephrine on the contractility of the hearts was studied during artificial stimulation.

It is demonstrated that in a normal heart 0.5 μg epinephrine injected into the canula leading to the heart causes an increase of contraction-height from 17 to 27 mm (on the curve) while the same dose of epinephrine given to a hypothyroid heart increases the amplitude from 15 to only 17 mm (on the curve). We finally studied the catecholamine content of the myocardium of 8 normal and of 8 hypothyroid rat hearts. The results of the nor-epinephrine analyses of the myocardial tissue are summarized in the diagram in Fig. 7.

A statistical significant difference between normal and hypothyroid hearts could not be demonstrated. The epinephrine contents are not shown in the diagram being nihil in both groups.

The histological slices made and studied by Dr J. Büller revealed a distinct difference between the structure of normal hearts tissue and of hypothyroid hearts tissue. The myocardium of the normal hearts was, apart from some edema inherent to the experimental procedure, quite normal while the myocardium of the hypothyroid hearts showed more edema, fibrosis and degeneration of the muscle fiber.

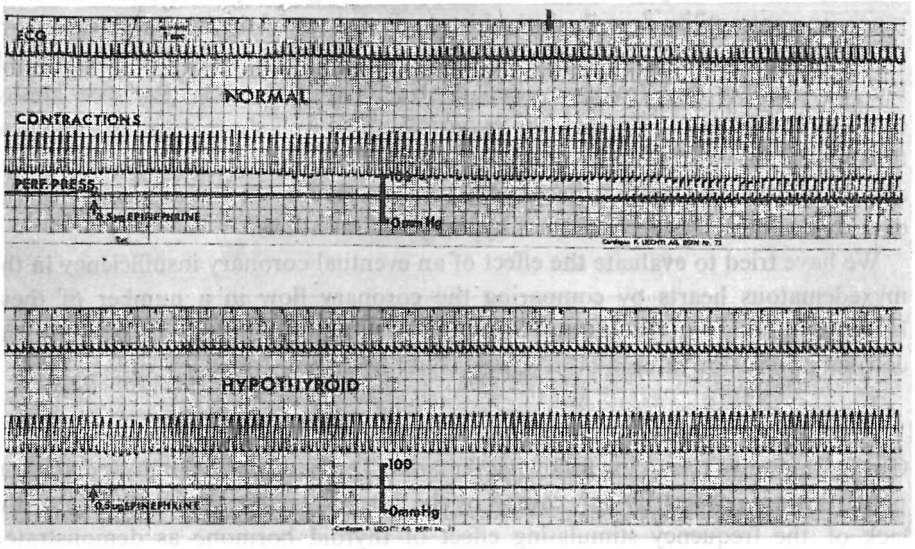

Figure 6

Electrocardiogram, contractions and perfusion pressure of a normal heart (upper curve) and of a hypothyroid heart (lower curve). 0.5 μg epinephrine causes an increase of contraction-height from 17 to 27 mm (on the curve) in the normal heart while the same dose of epinephrine given to a hypothyroid heart increases the amplitude from 15 to 17 mm (on the curve) only.

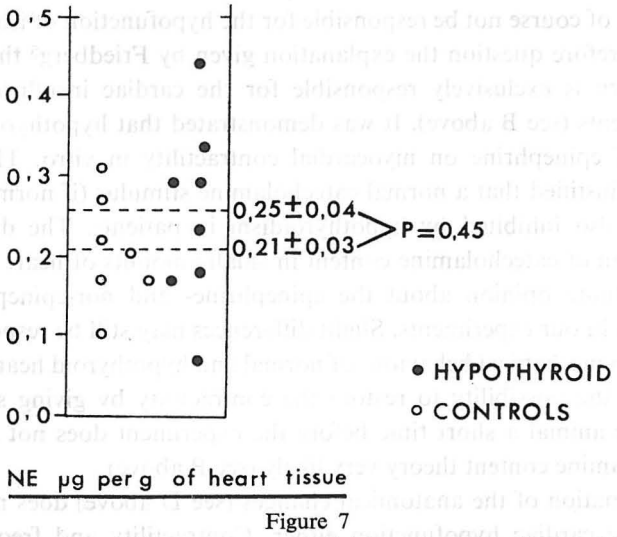

Figure 7

Nor-epinephrine content in μg pro gram myocardial tissue in perfused normal hearts (controls: open circles) and in perfused hypothyroid hearts (hypothyroid: closed circles). There is no statistical significant difference in nor-epinephrine content between the two groups.

Since these histological differences could be thought responsible for the differences in contractility described, the histological slices of the hearts derived from the hypothyroid rats injected with T3 before the experiment were also investigated. Despite the fact that frequency and contractility of these hearts were almost completely restored to normal, the myocardium as well showed the pathological findings of the hearts of the untreated animals. These findings suggest that the anatomical changes are not necessarily responsible for the low frequency or the disturbed contractile mechanism of hypothyroid rat hearts.

We have tried to evaluate the effect of an eventual coronary insufficiency in the myxedematous hearts by comparing the coronary flow in a number of these hearts with that of the normal hearts. No significant difference between the coronary perfusion rates in both groups could be demonstrated.

Discussion

Our findings give rise to the following remarks: The bradycardia in myxedematous patients is not necessarily only caused by the low body temperature but also by the lack of the frequency stimulating effect of thyroid hormone as demonstrated in this and other papers[3,4] (See A above).

The question whether or not Starling's law can explain heart failure in intact beings, falls outside the scope of this work[25].

Anyhow, it is demonstrated that under our experimental conditions a decrease of myocardial contractility can occur by lack of thyroid hormone only. Factors as decreased venous return, claimed to be responsble for cardiac failure in myoxedema patients, can of course not be responsible for the hypofunction of isolated perfused hearts. I therefore question the explanation given by Friedberg[5] that a decreased venous return is exclusively responsible for the cardiac insufficiency in hypothyroid patients (see B above). It was demonstrated that hypothyroidism inhibits the effect of epinephrine on myocardial contractility in vitro. The speculation seems to be justified that a normal catecholamine stimulus (if normal) on cardiac function is also inhibited by hypothyroidism in patients. The difficulties with the estimation of catecholamine content in small amounts of heart muscle do not justify a definite opinion about the epinephrine- and nor-epinephrine content of the hearts in our experiments. Slight differences may still be responsible for the differences in mechanical behaviour of normal and hypothyroid hearts.

However, the possibility to restore the contractility by giving small amounts of T3 to the animal a short time before the experiment does not seem to make the catecholamine content theory very likely (see B above).

The explanation of the anatomical changes (see D above) does not seem to be valid for the cardiac hypofunction either. Contractility and frequency can be restored to almost normal values without restoration of the pathological histological findings. A diminished coronary flow could not be demonstrated in the

hearts of the hypothyroid animals. So we can claim that heart failure in myxedema patients need not exclusively be due to coronary insufficiency[11].

Conclusion

Thyroid hormone of itself or via (unknown) intermediates can restore the inhibitory effect of hypothyroidism on rate and contractility of the heart.

Therefore cardiac failure in myxedema patients is more likely to be caused by lack of the action of the thyroid hormone on the myocardium than by other factors such as diminished venous return or catecholamine content of the heart muscle. The cardiac insufficiency in hypothyroid patients can, at least in part, be explained by the inhibitory effect of hypothyroidism on catecholamine stimulus.

Summary

The possible factors which may explain cardiac insufficiency in myxedematous patients are discussed. To evaluate these factors and to find out whether or not thyroid hormone influences cardiac function of itself, rate and contractility of isolated perfused hearts of hypothyroid rats were studied.

Hypothyroidism was achieved by thyroidectomy followed by administration of I^{131} and checked by P.B.I. estimation and I^{131} uptake. After the experiments the histology of the hearts was studied and the catecholamine content of the myocardium analyzed. It was found that heart rate and contractility have diminished in comparison to those of normal animals. Adding triiodothyronine (T3) to the perfusion fluid had no effect but intraperitoneal injection of small amounts of T3 a 1/2 to 1 1/2 hour before the perfusion experiment normalized the heart rate and the contractile mechanism almost completely. The catecholamine content of the heart muscle was found to be equal in both the normal and the hypothyroid rats. These findings demonstrate that current concepts about cardiac insufficiency in myxedematous patients are not likely to be true. Thyroid hormone is a specific factor which has a direct (or via unknown intermediates) important influence on rate and contractility of heart-muscle

Acknowledgement: The encouragement and advice of Prof. Dr. A. Querido, Prof. Dr. D. Durrer and Prof. Dr. H.A.H. Kassenaar are gratefully acknowledged. My thanks are due to my colleagues Drs. L.D.F. Lameijer, A. te Rijdt and J. Büller for their help with the experiments.

References

1. Matthes K.: Herz und Kreislauf bei Störungen der Schilddrüsenfunktion. Handbuch der Inneren Medizin. 4e Auflage. IX/4. Springer-Verlag, Berlin-Göttingen-Heidelberg, 1960.
2. Boyd G.S. en M.F. Oliver: Thyroid hormones and plasma lipids. *Br. Med. Bull.* **138**: 16, 1960.
3. Kruta V en J. Velicky: Ueber die Herzmuskelkontraktion nach der Schilddrüsenentfernung. *Kl. Wochenschr.* **36**: 1223, 1939.

4. PRIESTLEY J.T., MARKOWITZ J. EN MANN F.C.: The tachycardia of experimental hyperthyroidism. *Am. J. Phys.* **98:** 357, 1931.
5. FRIEDBERG CH. K.: Diseases of the Heart. 2nd ed. W.B. Saunders Comp., Philadelphia and London, 1958.
6. GOODKIND M.J., FRAM D.H. EN ROBERTS M.: Effect of thyroid hormone on myocardial catecholamine content of the guinea pig .*Am. J. Phys.* **201:** 1049, 1961.
7. HÖHFELT B.: Noradrenaline and adrenaline in mammalian tissues. *Acta Phys. Scand.* **25:** suppl. 92, 1951.
8. WHALEN W.J.: Apparent exception to the "All or None" Law in cardiac muscle. *Science* **127:** 468, 1958.
9. GAFFNEY Th.E., BRAUNWALD E. EN KAHLER R.L.: Effect of guanethidine or tri-iodothyronine-induced hyperthyroidism in man. *New Engl. J. Med.* **265:** 16, 1961.
10. ZONDEK H.: Das Myxoedeemherz. *Munch. med. Wochenschr.* **65:** 1180, 1918.
11. MCBRIEN D.J. AND HINDLE W.: Myxoedema and heart failure. The *Lancet* **7290:** 1066, 1963.
12. Meijler F.L., V.D. BOOGAARD F.V.D., TWEEL L.H. AND DURRER D.: Postextrasystolic potentiation in the isolated rat heart. *Am. J. Phys.* **202:** 631, 1962.
13. GIMENO A.L., GIMENO M.F. AND LEYDEN WEBB J.: Action of sexsteroids on the electrical and mechanical properties of rat atrium. *Am. J. Phys.* **205:** 198, 1963.
14. LANGENDORFF O.: Untersuchungen am überlebenden Säugethierherzen. *Pflüg. Arch.* **61:** 291, 1895.
15. MEIJLER F.L.: Over de mechanische activiteit van het geisoleerde, volgens Langendorff doorstroomde zoogdierhart. Master's Thesis, University of Amsterdam, 1960.
16. MEIJLER F.L., WIEBERDINK J. AND DURRER D.: L'importance de la position des électrodes stimulatrices au cours du traitement d'un bloc auriculo-ventriculaire postopératif total. *Arch. Mal. Coeur* **55:** 690, 1962.
17. VAN DER TWEEL L.H. AND STRACKEE J.: Electrische prikkeling van zenuwen en spieren. *Electrotechniek.* **5:** 84, 1955.
18. MEIJLER F.L. AND MEERSCHWAM I.S.: The action of metaraminol (Aramine) on myocardial contractility. *Acta Phisiol. Pharmacol. Neerl.* **11:** 418, 1962.
19. MEIJLER F.L., WILLEBRANDS A.F. AND DURRER D.: The influence of Polyvinyl Chloride (P.V.C.) tubing on the isolated perfused rat's heart. *Circulation Res.* **8:** 44, 1960.
20. VON EULER U.S. AND FLODING I.: A fluorometric micromethod for differential estimation of adrenaline and noradrenaline. *Acta Phys. Scand.* **33:** suppl. 118, 45, 1955.
21. KRUTA V.: Sur l'activite rythmique du muscle cardiaque. I. Variations de la réponse mécanique en fonction du rythme. *Arch.- Int. Physiol.* **45:** 332, 1937.
22. BLINKS J.R. AND KOCH-WESER J.: Analysis of the effects of changes in rate and rhythm upon myocardial contractility. *J. Pharm. Exp. Ther.* **134:** 373, 1961.
23. MEIJLER F.L.: Staircase, rest contractions and potentiation in the isolated rat heart. *Am J. Physiol.* **202:** 636, 1963.
24. PICKERING G.: Starling and the concept of heart failure. *Circulation* **21:** 323, 1960.