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The Role of the Aortic Pressure and Metabolic Factors in the Regulation of the Coronary Blood Flow

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Introduction

In a recent review (1) of the regulation of the coronary blood flow, while it has been pointed out that there is general agreement on the importance of the aortic pressure as a "driving force" for the blood through the myocardium, the type of relationship between the blood pressure and the coronary flow has been but poorly understood.

The reasons for this can be referred partly to experimental difficulties. The necessity of controlling as many variables as possible for the purpose of evaluating the various factors, which may or may not affect the coronary blood flow, often makes it necessary to use unphysiological preparations such as the isolated heart and heart-lung.

On the other hand, the so-called physiological preparations, e.g. the heart beating "in situ", while creating a situation where the humoral and nervous factors can play their normal role, does not generally allow as many parameters to be controlled as one would like. Thus only approximate deductions can be made.

Coronary Flow and Blood Pressure in Normoxia[1]

As a result of the earliest research both on the heart-lung preparation (15) and on the heart "in situ" (17), the blood pressure once seemed to be the most important factor in the regulation of the coronay blood flow on purely haemodynamic grounds. The importance of the blood pressure was stressed to such an extent also because of the fact that *Starling* and his pupils (16, 18, 19) were not able to show any effect of the cardiac output on the coronary blood flow in the denervated heart-lung preparation.

[1] This term is used to express the physiological conditions as to the arterial oxygen content and tension.

Recently an exponential relationship between the blood pressure and the coronary blood flow has been found in the isolated heart (20). Such a relationship must most likely be considered as the expression of the particular experimental condition, where the heart is not doing any external work, is removed from the usual nervous and humoral actions and is often exposed to a more or less severe degree of hypoxia. Under such conditions only some of the factors, one may suppose, are still operative, e.g. the heart rate, the consumption of oxygen, the metabolic products, the myocardial massaging action, the residual tonus of the coronary vessels, the nervous fibers and cells inside the heart, etc .

No similar relationship can be expected when the heart is "in situ" and acting as a self-perfusing system. In effect, the shape of the curve which should express the relationship of the blood pressure to the coronary flow shows a downwards concavity, this being just the opposite to what happens in the isolated heart (Fig. 1).

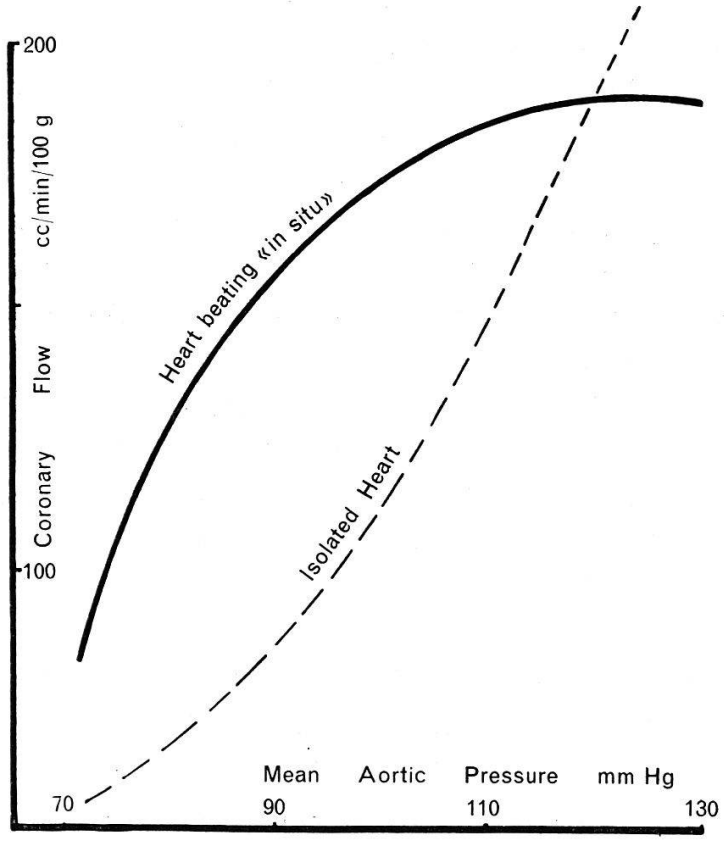


Fig. 1. Relationship between mean aortic blood pressure and coronary blood flow in the heart "in situ" and in the isolated heart.

This type of relationship in the heart "in situ" is found when mean values of experiments under standard conditions are pooled. However, the single values of the coronary flow for a given mean aortic pressure are widespread in several animals. Thus a consistent relationship between mean aortic pressure and coronary flow can not be found. This fact leads

to the conclusion that other factors are operating in the heart "in situ" at the same time as the blood pressure, especially those of a non-mechanical nature.

If, however, we take for granted that the curve obtained represents only the relationship between the haemodynamic effect of the blood pressure and the coronary flow, the different shape of the curves, as found in the isolated heart as well as in the heart-lung preparation points to the fact that the residual tonus of the coronary vessels is small, if not completely absent; and that the functional capacity of the vascular muscle cells is very poor indeed. This is in keeping with the recent conclusions of *Wezler* and *Sinn* on the pulmonary vessels (23).

Be that as it may, any study of the bearing of the blood pressure on the flow, in an organ undergoing rapid metabolic changes like the heart, must consider the interaction of the metabolism.

Already in 1931, *Rein* (21, 22) pointed out that the blood pressure seemed in the heart "in situ" to be less important for the regulation of the coronary blood flow than the work of the heart. Actually, the changes of the aortic pressure in the heart "in situ" run together with changes of the metabolism, as indicated by the increase or decrease of the consump-

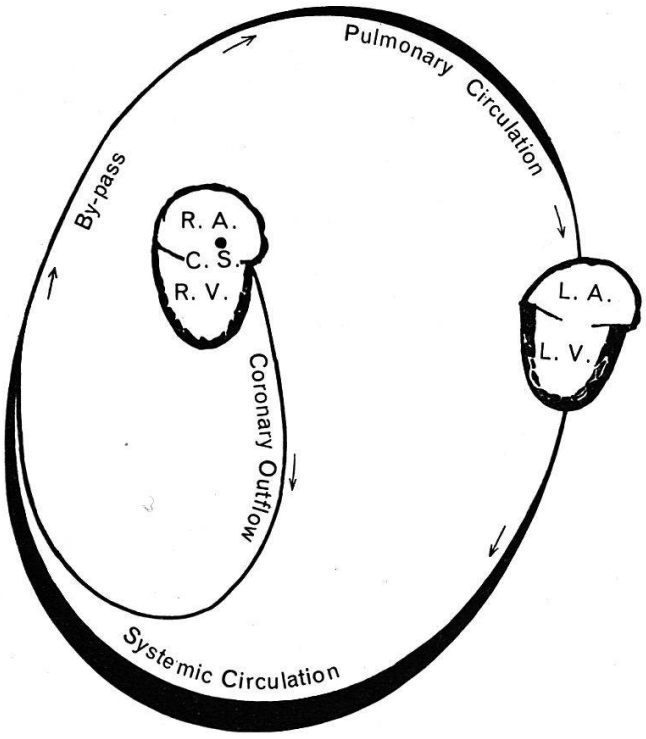


Fig. 2. By-pass of the right heart. The venous systemic blood goes directly to the pulmonary circulation without passing through the right heart. The venous coronary blood collects in the right heart and joins the systemic blood before reaching the pulmonary circulation. R. A., right atrium; R.V., right ventricle; L.A., left atrium; L.V., left ventricle. c.s., coronary sinus.

tion of oxygen and production of CO_2 (10, 12, 13). The question arises, of course, how much of the increase or decrease of the coronary flow depends upon the purely mechanical action of the blood pressure and how much upon the changes of the oxygen consumption.

The solution of such a question has been attempted by *Alella*, *Williams*, *Bohlene-Williams* and *Katz* in a quantitative way and with a new method (12, 13). In the dog's heart "in situ", the right heart was by-passed and used to collect only the venous coronary outflow (Fig. 2). Under this condition, 90% of the coronary inflow reaches the right heart mostly by means of the coronary sinus, the anterior cardiac veins and the Thebesian vessels. Furthermore, it is possible to change independently the amount and kind of the work of the heart, while it is still under the influence of the nervous and humoral factors.

The amount of the coronary blood flow which can be related only to the mechanical action of the mean aortic pressure is very small, as seen (Fig. 3) from the shape of the family of the oxygen isoconsumption lines;

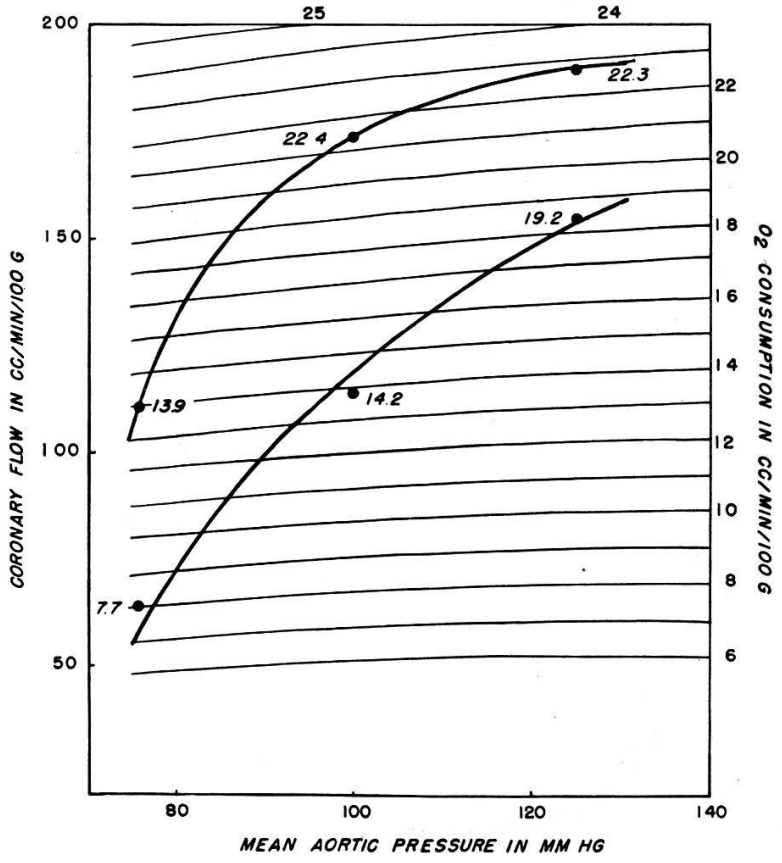


Fig. 3. Interrelationship between mean aortic pressure, oxygen consumption and coronary blood flow. The family of oxygen isoconsumption lines shows levels of coronary flow at theoretically constant myocardial oxygen consumptions (from 6 to 25 ml/min 100 g). – A different level of myocardial oxygen consumption means a different amount of coronary blood, whatever is the blood pressure within 80–140 mm Hg (*Alella* et al. [13]).

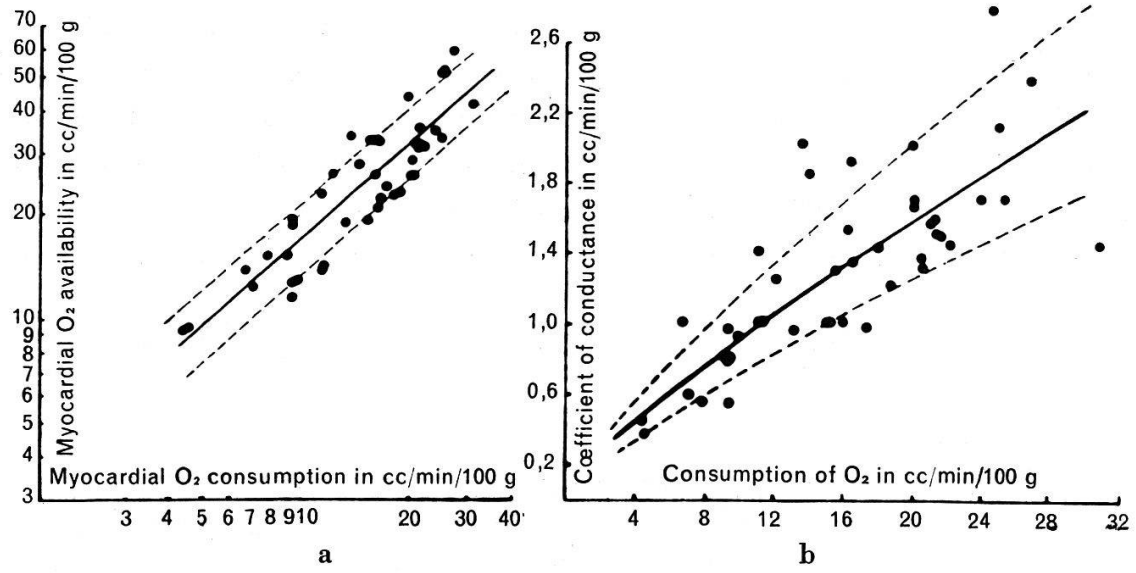


Fig. 4. – a) The availability of oxygen increases with the cardiac oxygen consumption. – b) A vasodilatation takes place with increasing cardiac oxygen consumption (*Alella* et al. [13]).

these express the changes of the coronary blood flow, after discounting the amount which can be explained by the myocardial oxygen consumption.

The apparent relationship of the mean aortic pressure to the coronary blood flow shows clearly that it is the integration of different levels of heart metabolism, since these curves run from the lowest to the highest level of consumption of oxygen. As a result, at the same level of a mean aortic pressure, different amounts of coronary blood flow can be found in close connection with the momentary level of oxygen consumption by the myocardium. As long as the arterial content of oxygen remains within physiological limits, the oxygen consumption of the heart is paralleled by the oxygen availability and the needs for oxygen are covered by means of a vasodilatation of the coronary vessels (Fig. 4 a and b).

The inter-dependence of the coronary flow and the consumption of oxygen allows the coronary flow to be forecast on the bases of the oxygen consumption alone: a fact which is not possible to all intents and purposes by using the blood pressure. Thus the oxygen consumption of the heart "in situ" is revealed to be more important for the regulation of the coronary blood flow than the blood pressure, when the changes of the latter occur within a physiological range.

Coronary Flow and Blood Pressure in Hypoxia

In acute hypoxia, where the heart undergoes a particular stress, there is an increase both of the blood pressure and the coronary flow (1, 2, 3, 4, 5, 6, 7, 8). In such a condition, the decreasing arterial oxygen brings about complex changes of the dynamics and metabolism of the heart.

The apparent relationship (10) between mean aortic pressure and coronary flow shows the same trend as in normoxia, if considered at several constant degrees of arterial oxygen saturation (Fig. 5). The decreased amount of oxygen produces a shift of the curves, which express the aforementioned relationship, the amount of coronary blood flow for a given blood pressure being bigger as the degree of saturation lessens.

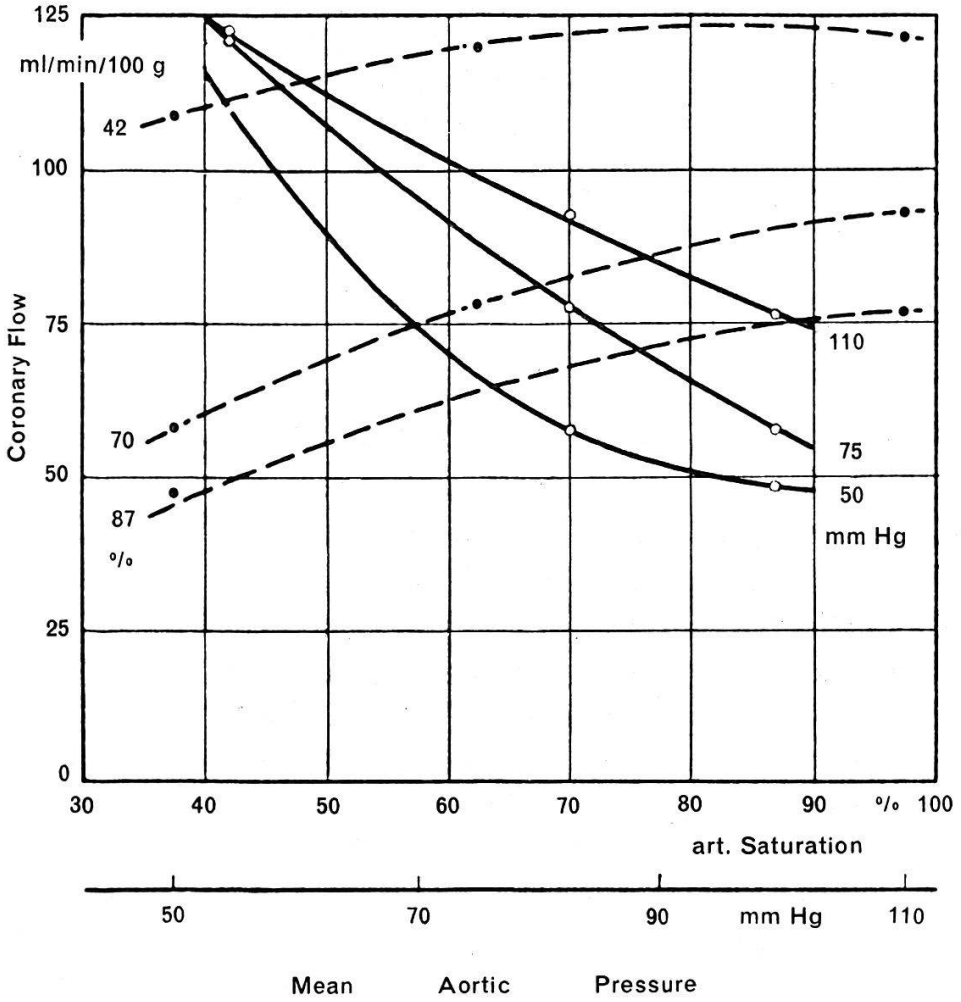


Fig. 5. At three constant hypoxic levels of arterial saturation (42, 70, 87%) the coronary blood flow increases with the mean aortic pressure. The decrease of arterial saturation causes the coronary flow to increase at three constant values of mean aortic pressure. *Alella* [10]).

In any case, the increase of the aortic pressure causes the heart to have a greater need of oxygen, as shown clearly in the Fig. 6, where a greater consumption of oxygen is to be found with the higher blood pressure levels at two different degrees of arterial blood saturation. Thus the increase of the aortic blood pressure really means at the same time both an improved aortic head-pressure and a metabolic surcharge, when the myocardial oxygen availability and extraction decrease linearly with the arterial saturation (3, 9, 10, 11) (Fig. 7).

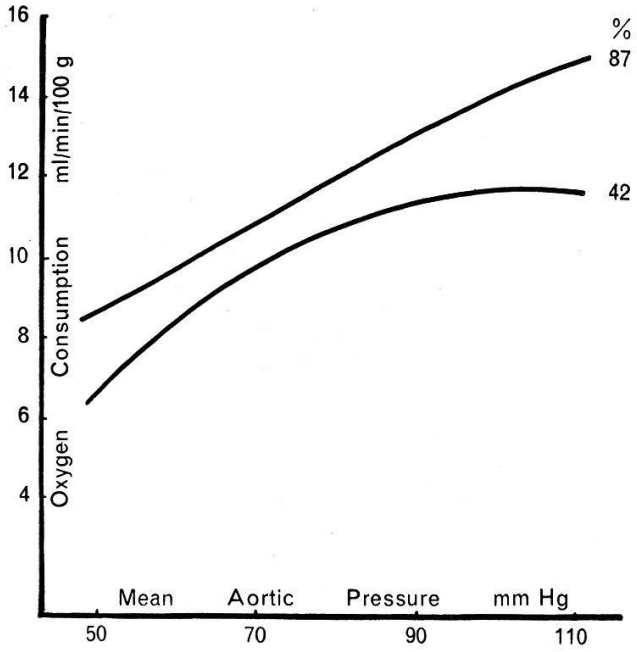


Fig. 6. The myocardial oxygen consumption is greater with increasing blood pressure at two hypoxic levels (42, 87%) of arterial saturation.

The adjustment of the coronary circulation to the hypoxic conditions is accomplished by means of a vasodilatation of the coronary vessels, as a consequence of the dropping myocardial oxygen tension.

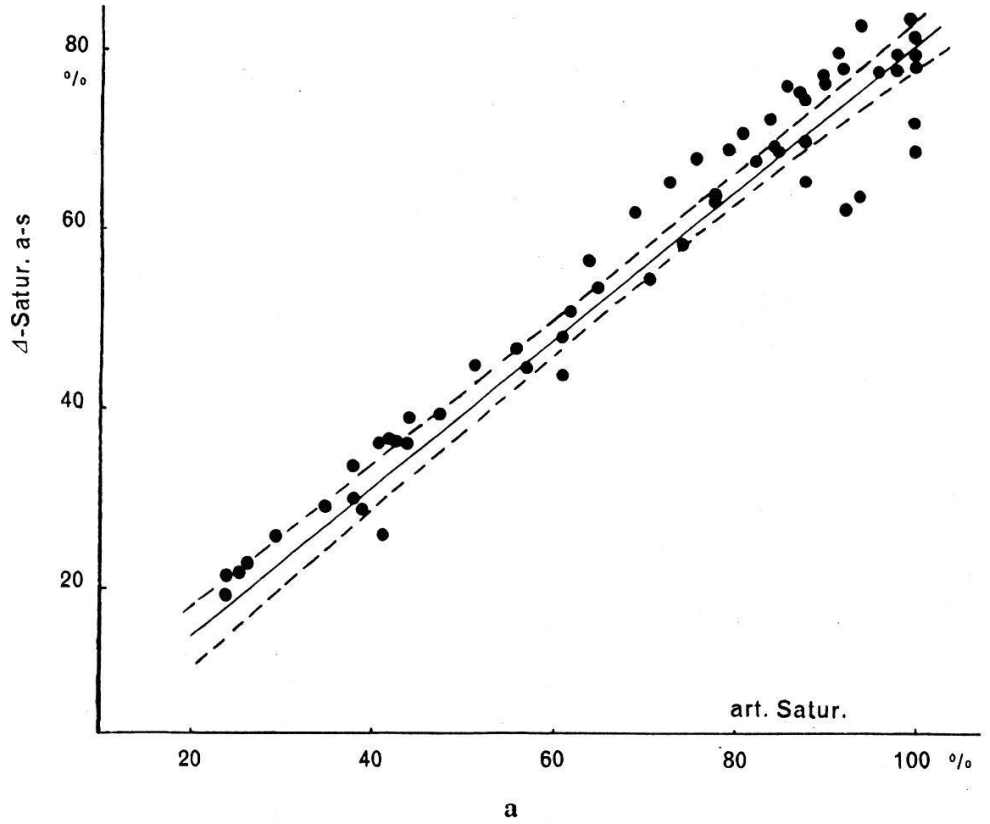
This vasodilatation attempts to cover the oxygen needs of the heart by increasing the amount of blood circulating through the coronary vessels. With the further fall of the arterial oxygen content, the heart gets into such a condition that the balance between oxygen availability and demands reaches its breaking point and the heart fails (1, 10).

Conclusions

In normoxia, as well as in hypoxia, other factors of a non-mechanical nature attain an importance as seen from the experimental results referred to.

The heart has to be considered as a working muscle with a high need for oxygen, and as an organ whose oxydative way of freeing energy is the preferred one, as long as enough oxygen is at its disposal (9, 13). In effect, a high extraction and utilisation of oxygen (almost 80% [1, 9, 10]) is found and the "myocardial oxygen reserve" (9, 10) is not used, the oxygen needs being covered by means of an adjustment of the coronary flow by vasodilatation.

The extraction of oxygen is already at its limit and does not offer any further possibility of covering the oxygen needs of the heart. Actually, with a normal arterial oxygen, the oxygen content and tension of the venous coronary blood are practically constant, a decrease being brought



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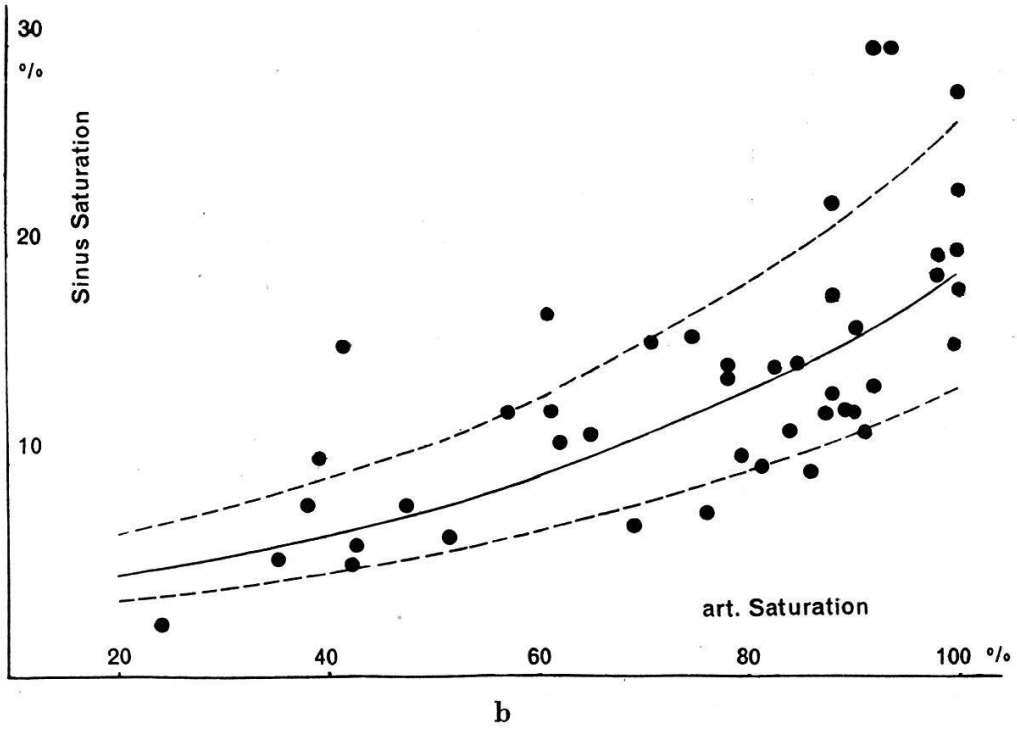

b

Fig. 7. – a) Reduction of the cardiac oxygen extraction with the decreasing arterial saturation. – b) The oxygen saturation of the coronary sinus blood lessens with the arterial saturation (*Alella* [9]).

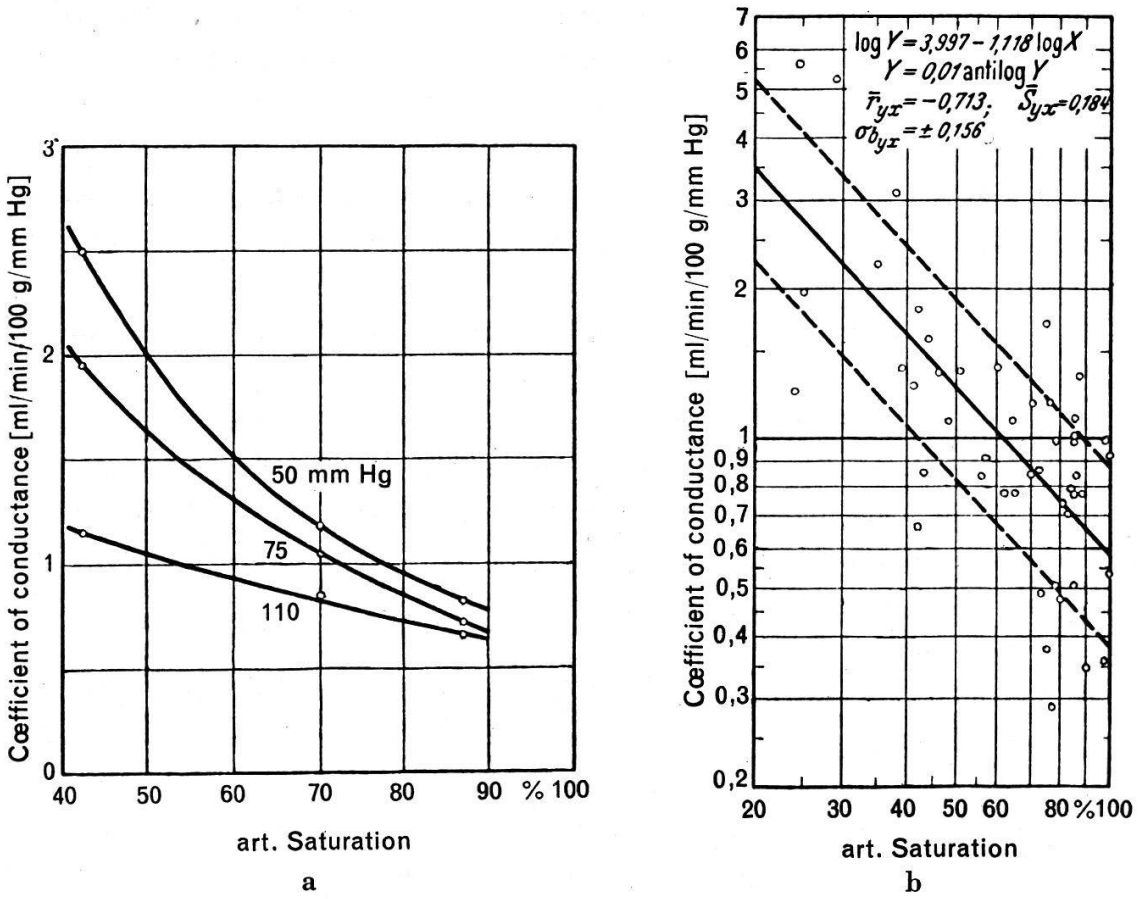

Fig. 8. – a) A dilatation of the coronary vessels attempts to cover the oxygen needs of the hypoxic heart, whatever is the mean aortic pressure (from 50 to 110 mm Hg). – b) Relationship between arterial oxygen saturation and coefficient of conductance of the coronary system (*Alella* [10]).

about only in hypoxia, essentially as a consequence of the decrease of the arterial saturation (8, 10).

In hypoxia the decreased myocardial oxygen tension seems to be the "pilot factor" for the release and graduation of the dilatation of the coronary vessels, the local events within the myocardium being more important than the changes of the mean aortic pressure.

When hypoxia, however, is not present and the heart has a normal availability of oxygen, the vasodilatation of the coronary vessels is still the most important mode of adjustment of the coronary circulation to the oxygen needs of the heart.

Some experimental facts suggest that the myocardial oxygen tension may in physiological conditions be already almost at the critical point. Small decreases of that tension could be, therefore, effective in producing vasodilatation. If this turns out to be true, no difference would exist between the hypoxic and normoxic vasodilatation, as to the mechanism of production, the changes of the myocardial oxygen tension being the common factor in both cases. Yet, for the sake of distinguishing between

the normoxic and hypoxic vasodilatation, the former can be defined as primary, being caused by local events within the heart, while the latter can be called secondary, the cause being the falling arterial content of oxygen.

As a matter of fact, the real mechanism of action of the reduced myocardial oxygen tension is a ground for speculation. There are the following possibilities:

1. a direct action of the oxygen on the muscle cells of the vessels and/or on the capillaries.
2. an indirect action through nervous cells and fibers and/or receptors.
3. and/or a local release of substance(s) such as hormones or metabolites.

It must be emphasized, however, that the coexistence of the action of several factors is proved by some experiments (8), e.g. the sympathetic stimulation and the hypoxia together have a cumulative effect on the coronary vessels.

At all events, it seems clear that it is necessary to refer the values of coronary blood flow to the myocardial oxygen consumption and availability in addition to the mean aortic pressure, as is usually done, the functional meaning of the coronary blood flow thus being obvious (1).

Finally, while many points of the regulation of the coronary blood flow have of late been investigated, it must nevertheless be stressed that on many questions we are still groping in the dark and further research is necessary.

Summary

Although it is a well established fact, that the aortic blood pressure is one of the determining factors of the coronary blood flow, the type of relationship has been but poorly understood.

Recently an exponential relationship has been found on the isolated heart and deducted on theoretical bases. This kind of relationship is to all intents and purposes non-existent when the heart is "in situ" and acting as a selfperfusing system. Thus other factors gain importance besides the mean aortic pressure, e. g.: nervous, humoral and metabolic influences; changes of the level and kind of the heart work.

In effect, an increasing or decreasing mean aortic pressure produces parallel changes of the metabolism of the myocardium, as expressed by an increase or decrease in the consumption of O_2 and in the production of CO_2.

If, under such conditions, the consumption of oxygen is taken in consideration, the values of coronary blood flow are closer related to this factor than to the mean aortic blood pressure.

The oxygen needs of the myocardium are satisfied by means of a vasodilatation, when normal quantities of oxygen are at the disposal of the heart.

In hypoxia the vasodilatation of the coronary vessels attempts to cover the oxygen needs of the heart and its effectiveness is determined by the decrease of the myocardial oxygen tension rather than by the increase of the mean aortic pressure.

Zusammenfassung

Obwohl es allgemein bekannt ist, daß der Blutdruck in der Aorta einer der bestimmenden Faktoren für die Coronardurchströmung ist, wurde die Art der Beziehung zwischen beiden noch wenig untersucht. Kürzlich konnte eine solche Beziehung am isolierten Herzen gefunden und ihre theoretische Grundlage ermittelt werden. Diese Art des Zusammenhanges ist aber bei allen Untersuchungen nicht vorhanden, wenn das Herz in situ verblieben ist und als ein Organ tätig ist, das gewissermaßen sich selbst durchströmt. Daher bekommen andere Faktoren als der mittlere Aortendruck mehr Bedeutung, wie z. B. nervale, humorale und stoffwechselbedingte sowie Veränderungen der Menge und Art der Herzleistung. Tatsächlich verursacht ein an- oder absteigender mittlerer Aortendruck gleichlaufende Änderungen im Stoffwechsel des Myokards, die sich in einer Vermehrung oder Verminderung des Sauerstoffverbrauches oder der CO_2-Ausscheidung äußern. Wenn unter solchen Bedingungen der Sauerstoffverbrauch beobachtet wird, so zeigt sich, daß die Werte der Coronardurchströmung enger diesem Faktor gleichgeordnet sind als dem mittleren Aortendruck. Der Sauerstoffbedarf des Myokards kann durch gefäßerweiternde Mittel befriedigt werden, wenn normale Sauerstoffmengen dem Herzen zur Verfügung gestellt werden. Bei Sauerstoffmangel wird durch die Coronargefäßerweiterung der Sauerstoffbedarf des Herzens gedeckt. Diese Gefäßmotilität wird also mehr durch das Absinken der Sauerstoffspannung im Herzmuskel als durch das Ansteigen des mittleren Aortendruckes bestimmt.

Résumé

Il a été établi que la pression artérielle aortique est un des facteurs déterminants du débit coronarien; toutefois, les modalités de cette relation ne sont que très mal connues.

On a récemment trouvé une relation exponentielle en étudiant le cœur isolé et en partant de raisonnement théorique. En fait, cette relation n'existe pas, lorsque le cœur est «in situ» et qu'il fonctionne comme système

«d'autoperfusion». Ainsi, d'autres facteurs prennent de l'importance à côté de la pression aortique. Ce sont les influences nerveuses, humorales et métaboliques; changements de concentration et de modalités sur le travail du cœur. En fait, une simple augmentation ou diminution de la pression aortique produit des modifications parallèles dans le métabolisme du myocarde, qui se manifestent par une augmentation ou une diminution dans la consommation de O_2 ainsi que dans la production du CO_2.

Dans ces conditions, si l'on prend en considération la consommation d'oxygène, le *taux* du débit coronaire sanguin est en relation plus étroite avec ce facteur qu'avec la pression aortique. Les besoins d'oxygène du myocarde sont satisfaits par la vasodilatation, lorsque des quantités normales d'oxygène sont à la disposition du cœur.

En hypoxémie, la vasodilatation des vaisseaux coronaires cherche à couvrir les besoins d'oxygène du cœur et son efficacité s'apprécie par la diminution de la tension d'oxygène plutôt que par l'augmentation de la pression aortique.

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