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CARDIOVASCULAR AND RESPIRATORY PHYSIOPATHOLOGICAL ASPECTS OF HYPOKINESIA

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Translation of "Su alcuni Aspetti di Fisiopatologia cardiovascolare e Respiratoria nella ipocinesia", **Recenti Progressi in Medicine (Roma), Vol. 52, No. 4, 1972, pp 323-344**

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16. Abstract

This article is a lengthy discussion of the many effects of hypokinesia on the human organism.

The difference in normally mobile subjects and hypokinetic subjects as relates to:

1. Heart rate
2. Average humeral pressure
3. Cardiac capacity
4. Cardia index
5. Systolic range and
6. Large cycle resistances are presented.

The article concludes that further studies must be carried out in seven specific areas of cariocirculatory damage due to hypokinesia.

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From ancient times we have known that the function of an organ increases with use, and that "we lose what we do not use". Although rest may be a protection for a diseased organ, it induces a progressive reduction of the functional capacity of normal organs which depends, within physiological limits, on the intensity and the frequency of the latter's activity. Prolonged limitation of muscular activity generates significant deterioration of organs and systems and especially the cardiovascular system. This general phenomenon is commonly known. On the other hand, much less is known on the correlations between the frequency, intensity and duration of the inactivity and the qualitative and quantitative modifications of the cardiovascular functional capacity. */323

The want of physical exercise resulting from motorization, automation and the almost universal possibility of applying a number of instruments eliminating man's muscular activity has become one of the most important characteristics of western civilization of the 20th Century. The relationships between cardiovascular activity and the reduction of physical exercise, although they have been the object of attention in recent years, have not been studied systematically so far so as to clarify the intimate mechanisms correlating them and most of the authors have performed partial studies following a single direction of investigation and thus losing the overall view of the problem. It had been suspected for a long time that the want of physical exercise was one of the most important causes of the increase of degenerative cardiovascular diseases in western countries. It is truly inexplicable why, in spite of the interest aroused in this area and the statistical evidence of the relationships between physical inactivity and degenerative cardiovascular diseases, so few attempts have been made to clarify the physiopathological significance of hypokinetic cardiovascular diseases.

On the other hand, the study of hypokinesia, that is, the pathology related to immobility, has become of vital importance today, not only because, as we said, modern man is using increasingly the machines he

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*Numbers in margin indicate pagination of foreign text.

built, but also because immobility represents a fundamental situation for the astronaut. Indeed in space flights, man is exposed to a considerable reduction of muscular activity, both because he is confined to a narrow cabin and because the absence of body weight reduces the work to accomplish movements. Moreover, the endovasal hydrostatic solicitation acting continuously in life on Earth, when man is in an orthostatic or seated position, is eliminated by which the conditions, although profoundly different in other aspects, are similar to those of man at rest in a clinostatic position. Therefore, the knowledge derived from the studies on muscular inactivity will also contribute extensively to a more critical evaluation of the variation of the physiological parameters observed during prolonged weightlessness in space flights. /324

Meanwhile, the protective value of physical exercise on the heart and, in particular, in the myocardiopathies on a hypoxic base, has been known for some time from the many epidemiological and anatomophysiological studies. On the other hand, as we said, little is known on the effect of muscular hypoactivity on the cardiovascular functions.

We ourselves about 2 years ago, in a paper presented at the 30th Congress of the Italian Society of Cardiology, noted that muscular work, because of the deep modifications induced in the local circulation, has an extraordinarily favorable effect on the circulatory flow of areas affected by obliterating arteriopathy. We emphasized then that, like the cardiopathies caused by degenerative causes, obliterating arteriopathies are a frequent disease of modern man because of the increasingly reduced activity of the muscles which, as we learn in physiology, is the most powerful stimulus to the increase of the circulatory flow.

It is certainly not correct to take the physiopathological modifictions, observed in healthy subjects exposed in acute immobilization conditions for short periods of time, to explain in all its aspects the pathology which seems to be realted, at least in part, to chronic reduction of physical exercise. Furthermore, the vast differences in objectives and methods, especially as regards the degree and duration of immobilization, make it difficult to compare the results obtained.

Many experiments were carried out for the particular purpose of investigating the metabolic effects of immobilization, but most of them contain scanty data on the circulatory effects. Scientists examined the combined effects of immobilization and weightlessness by immersion in water in an attempt to simulate conditions occurring during space flights, but most of these studies concern primarily the hemodynamic reactions to orthostatism, and furnish but little other data on the behavior of the circulatory system. /325

Although not extensive, the data regarding the physiopathological effects are already sufficient to be able to establish some basic points of the physiopathological modifications of the cardiovascular system. In 1929, Cuthbertson [1] was the first to conduct studies on the effects of prolonged rest in bed of healthy subjects, but his observations concerned mainly metabolic effects. Subsequently, Taylor et al [2] were the first to study the modifications of the cardiovascular system in subjects kept in bed for 3 to 4 weeks and who had permission to get up only once a day for 10 minutes. At first they noted an average increase in the heart rate of 0.41 beats per minute per day in the morning, and 0.67 beats per minute in the evening. It should be stressed that the same authors, Taylor et al, observed a disproportionate increase of the heart rate during work, and that this response persisted for 16 days after resumption of muscular activity. This is an observation which, as will be enlarged upon later, shows the poor adaptation of the cardiovascular system of the hypokinetic subject to increased requirements imposed by muscular work.

All the studies conducted successively agree in the finding of tachycardia in subjects during muscular inactivity. Indeed, even in the classical study by Deitrick et al, it was noted that, in their hypokinetic subjects, tachcardia was found at rest and there was an excessive increase of the heart rate during physical exercise, persisting for 6 weeks after the end of the exercise. Increase in the heart rate was observed by Beckman et al [4] in a subject immersed in water for 23 hours and by Graveline et al [5,6] who emphasized that the tachycardic response was earlier and more intense in subjects during their

immersion in water. But it should be noted that in the experiments of Vallbona [7], already after 3 days of bed rest, they observed a considerable increase of the heart rate combined with more intense nychtemeral fluctuations and the occurrence of respiratory arrythmia. The observations of Saltin et al [8] and Raab et al [9] (the latter noted that the heart rate registered in 266 subjects, varied conversely to the extent of their usual physical activity) are consistent with the observations of Taylor et al [2].

It is, therefore, possible to say that during physical inactivity there is tachycardia which, as will be specified more precisely, expresses the typical sympathetic hypertony of inactive subjects-- /326 this neurovegetative behavior being totally opposite of what is found in trained subjects in whom one finds predominantly the vagal tonus-- and bradycardia occurs. But a very important modification which is responsible for many cardiocirculatory functional responses of the hypokinetic subject is the reduction of the cardiac capacity. Taylor et al [11] had already noted the reduction of the circulatory flow, though usinng a radiological procedure of low reliability. But Holmgren et al [12] also observed in this manner a reduction in the circulatory flow in hypokinetic subjects and emphasized the clcse relationship between the reduction of the circulatory flow and the cardiac volume. Saltin et al [8] also revealed a reduction of the cardiac capacity at the end of a period of immobilization. It is clear that, although adrenergic hyperactivity can account for the tachycardia, there is still contrast with the reduction of the circulatory flow, which should, on the contrary, increase the well known positive inotropic effect of sympathetic hypertony. But an increase of the cardiac capacity during adrenergic hypertony can only occur if there is adequate venous return, which on the contrary is significantly reduced during inactivity for many reasons which will be subsequently described. This also means that the reduction of the plasma volume which takes place during inactivity may also justify partly the reduction of the circulatory flow occurring in subjects after prolonged inactivity. It should also be stated that, if the reduction of the circulatory flow in hypocinesia is the result of the reduction of the functional performances on the part of the myocardium, but also

a qualitative reduction because of modifications at the cellular level. Consequently, with the circulatory flow decreased and the heart rate increased, the systolic range decreases. Thus, this is a functional behavior totally opposite to what occurs in muscular training in which, as we know, the systolic range is higher because of bradycardia with the maintenance of a normal circulatory flow.

Another parameter we must take into consideration is the systemic arterial pressure. Graveline et al [5,6,13] noted that after immersion in water for 7 days they noted a reduction of arterial pressure with unchanged differential pressure. A modest reduction in average pressure was noted by Deitrick et al [3] and by Taylor et al [14] in their subjects placed in bed rest. Similar modifications, but earlier and more extensive, were noted by Graveline et al [5,6] in their subjects during /327 immersion in water. In the experiments by Vollbona et al [7], after 2-3 day periods of bed rest they noted a slight tendency to the reduction of systolic arterial pressure, without modifying the systolic ones, which the authors consider a manifestation of a return to normal values from the higher ones found at the beginning of the experiment, rather than a real drop. Moreover, they found only a slight increase of the average arterial pressure in subjects exposed to bed rest for 14 days.

Table 1. Average values obtained in 32 "normally mobile" and 22 "hypokinetic" subjects

	normally mobile subjects	hypokinetic subjects
heart rate (minutes)	74	84
average humeral pressure (mm Hg)	90	93
cardiac capacity (ml/min)	5180	3970
cardia index (ml/min)	3050	2335
systolic range (ml)	70	47
large cycle resistances (dyne/sec/cm^{-3})	1390	1875

Our observations in subjects treated clinically for minor diseases without involvement of cardiovascular and respiratory system, who kept to their bed over long periods of time varying from 30 to 45 days, are

consistent in showing the want of obvious changes in the average pressure of the large cycle. In hypokinetic subjects, as for the rest of our subjects confined to bed over a long period, a value of the cardiac index is noted below those obtained in subjects during normal activity. It will thus be understood that the want of a drop of the average arterial pressure may be a consequence of an increase of the large cycle resistances (table 1). The fact that there is an increase of the circulatory resistances is proved not only by our observations, but by those of Vallbona et al [7] on the speed of the pulse wave, studied in subjects in bed rest, which showed a progressive increase with the progress of inactivity. This is probably related to the increase in the /328
peripheral resistances as a result of the adrenergic hyperactivity. This means that the increase of the peripheral resistances causes an increase in the propagation speed of the pulse wave through the arterial system. Therefore, the rate of the pulse wave would be a perceptible indicator of the increase of the peripheral resistances which cannot be revealed by an increase in the systemic arterial tension conditions because of the reduction of the circulation flow. But the increase in the circulatory resistances may also depend in part on hemoconcentration occurring during inactivity, thus causing increase of hematic viscosity which induces in its turn, by virtue of the Poiseuille law, increase in the circulatory resistances. Indeed, there are many authors (Deitrick et al [3], Whedon et al [15], Spealmann et al [16], Widowson and McCance [17], Graveline et al [5,6,13,18], Taylor et al [2], Miller et al [10], McCally [19]) who observed muscular hemoconcentration with a drop in the plasma volume in subjects in the hypoactive state. In reality, after a few hours of rest in bed, there is initial hemodilution with a drop in the hematocrit (by increasing the volume of plasma) with rapid return to normal values and subsequent increase (by reduction of plasma volume) after 24 hours or more inactivity. Hemoconcentration may depend on the increase of the urinary flow which was attributed to an inhibition of the antidiuretic hormone and aldosterone by increasing the blood volume in circulation, occurring at the beginning of bed rest or immersion in water [18]. It may be postulated that modifications in aldosterone secretions are caused by variations of the distension of the right atrium. But it may be emphasized that Gawenlock [20] did not

record any variations in the urinary secretion of aldesterone in inactive subjects. On the other hand, hemoconcentration is the opposite to what happens during muscular activity. Indeed, Taylor et al [2] and Miller et al [10] observed in subjects, after 4 weeks of nonambulation, an increase in plasma volume and a decrease in the red corpuscles. This is partially consistent with the experimental data of Broun [21] who found in dogs, during muscular activity following inactivity, a destruction of red corpuscles. Therefore, the inactivity factor itself gives modifications different from those observed in subjects placed in an environment simulating a space cabin in which we find a reduction of hemoglobin and of the hematocrit with reduction of blood and plasma volume. Obviously, in the environment simulating the space module, other factors are involved in the determination of these hematic changes. In this connection we would say that in the /329
literature some variations in the physiological parameters have been attributed often to hypokinesia present along with other conditions (for instance, hyperoxia) capable in themselves of modifying the above mentioned parameters. Therefore, the increase of the resistances of the major circuit should be attributed to two facts: sympathetic hyperactivity and in part, though to a lesser degree, the increase of hematic viscosity. But it should be stressed that even in hypokinetic subjects there is adequate adaptation of the major circuit to the increase of flow imposed by muscular work. In this connection, we would like to discuss the behavior of the cardiovascular system of the hypokinetic patient under muscular work.

We wish to note above all that there are few observations in this area and we believe that we have brought a contribution, if a modest one, to this problem by studying certain hemodynamic and respiratory, as well as hematochemical parameters in subjects undergoing long bed rest, studied during maximum and submaximum muscular work. In accordance with the data of Taylor et al [2,14], Miller et al [10], Saltin et al [8], Birkhead et al [22], we made in particular the following observation: reduction of the maximum consumption of O_2. This finding is consistent with the values observed by us of significantly lower cardiac flow in these subjects at maximum exercise level. Meanwhile,

we note a greater increase of the heart rate with consequent lesser increase of the systolic range (Figures 1, 2, 3). At the same time, we observe also for muscular work corresponding on the average to 40% of the maximum VO2, and representing an O2 consumption around 900 ml, a considerable increase in arterial lactacidemia, whereas from the classical literature data [23] it appears that hyperlactacidemia in normal subjects occurs for work corresponding to a VO2 of 1200 ml [24,25]. Furthermore, the different functional adaptation of the hypokinetic subjects is also estimated in the observation of the behavior of lactacidemia of venous blood coming from a muscular area under activity.

Indeed, both the artery-vein difference in lactic acid of the lower limbs (blood taken by means of venous retrograde catheterization from the femoral vessel, below the point of discharge of the great saphenous vein) when the subjects work with the lower limbs and the artery-vein difference of the upper limbs (blood taken by means of venous retrograde catheterization, from the axillary vessels) when the subjects work with the upper limbs, showed a clear negative effect.

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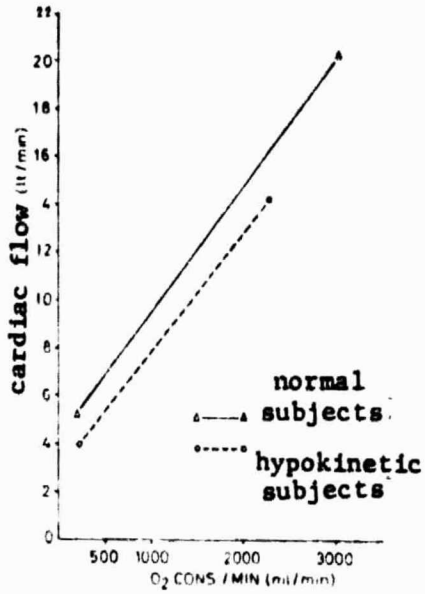
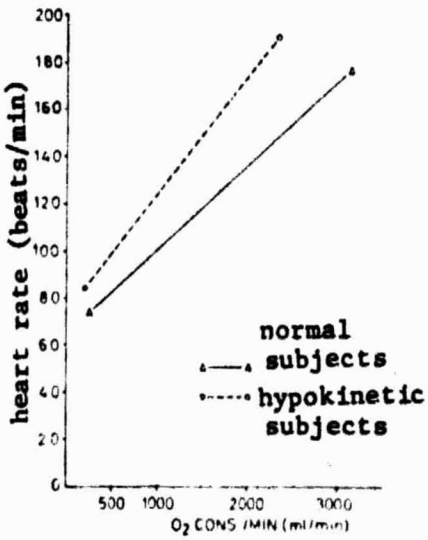


Figure 1



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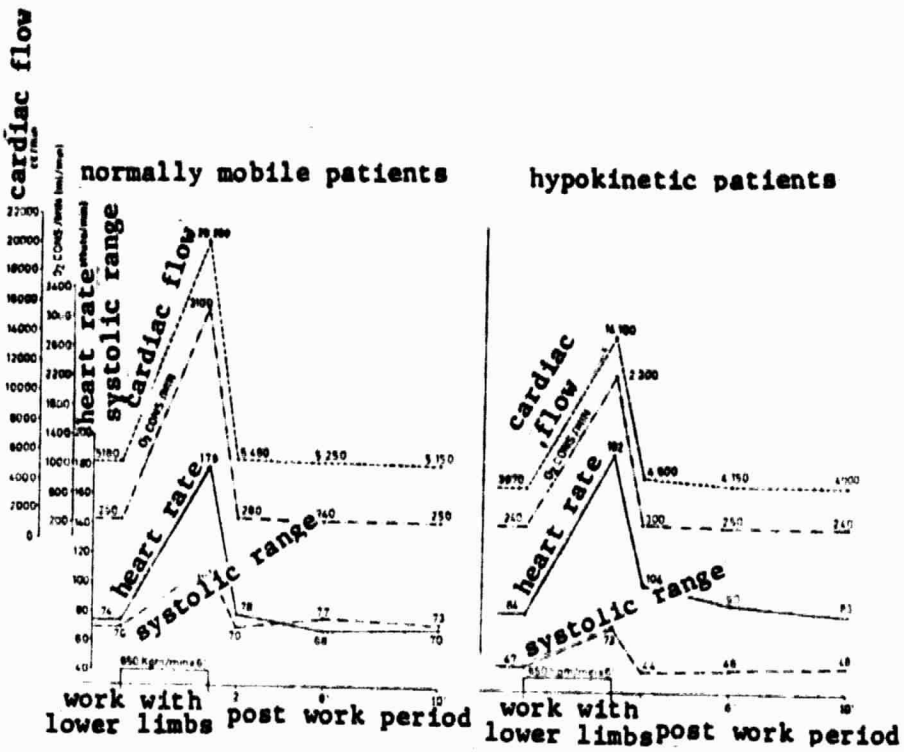

Figure 3

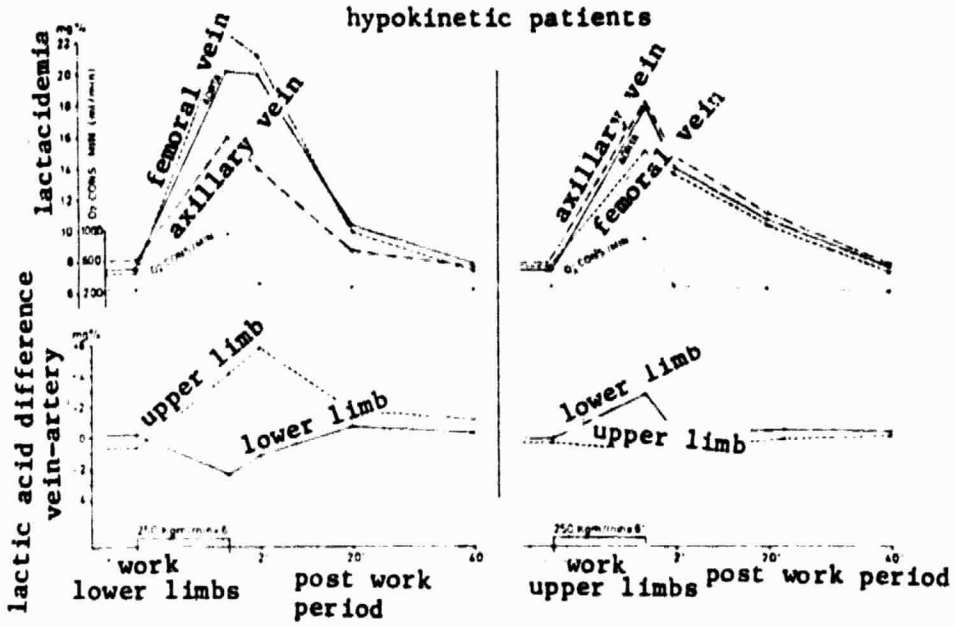

Figure 4

The different functional adaptation is also appreciated when we observe the behavior of arterial and venous lactacidemia in the post work period. Indeed, we find in these subjects a slow return (within 40 minutes) to the basic values (Figure 4). /331

These data show the reduced adaptability of hypokinetic subjects to muscular work, because of an inadequate increase of the circulatory flow with rapid depletion of the internal oxidative sources and with probably more intense coparticipation energy-wise of anaerobic glycolyses. Even the greatest decrease of 0_2 saturation of venous blood coming from an active muscular area, shows the lack of adaptation of the cardio-circulatory system to muscular work. Indeed, hypokinetic subjects show more intense 0_2 desaturation of the venous blood flowing back from the working limbs, with simultaneous increase of the arteriovenous difference in 0_2, which gives a higher value of the local CUO (Figures 5,6,7).

This is probably a consequence of the lower local flow because of which the tissue extracts the largest possible amount of 0_2 reaching it, perhaps also by a slowing down of the flow and higher acidity of the venous flow. In this connection, we recall that using a formula* already adopted by Carlson and Pernow [26,27] to estimate the local flow in which it is postulated that the increase of 0_2 consumption above the value at rest is due entirely to the increased utilization of the latter in the working tissue, we obtained significantly reduced values. But this reduction is evaluated taking into account the limitation of the formula adopted. Probably the absence of reduction of the circulation flow observed by Browse [28] is due to the too short period of rest (from 12 hours to 5 days) of his hospitalized subjects. We find the author's conclusion, that the demineralization of the bone and the reduction of the muscular mass occurring in inactivity is not the result of a reduction of the circulation flow of the inactive extremities too risky. In this connection, furthermore, it should not be /332 /333

* $$\frac{\text{Consumption } 0_2 \text{ during work} - \text{basic } 0_2 \text{ consumption}}{\text{Difference of local } 0_2 \text{ A - V}}$$

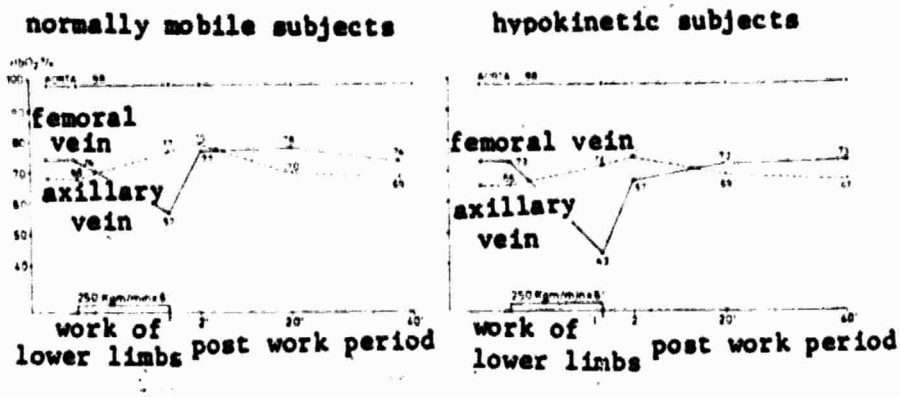

Figure 5

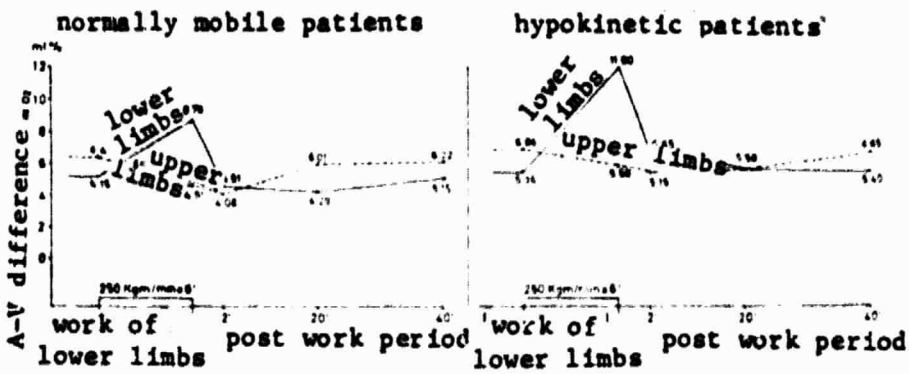

Figure 6

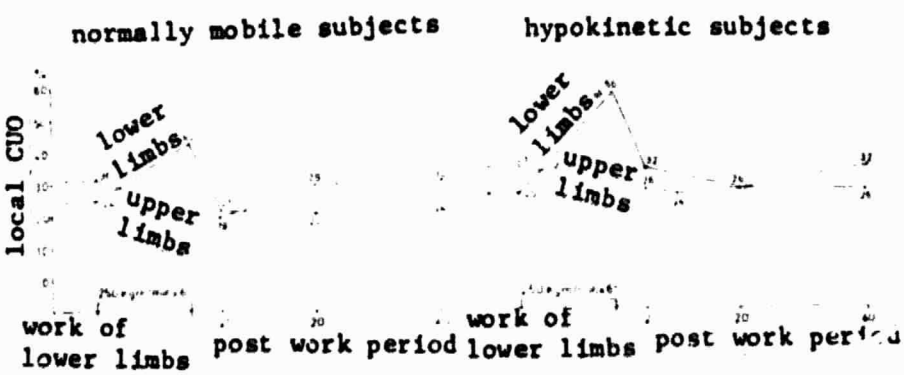

Figure 7

forgotten that possible modifications of the peripheral circulation may occur during muscular inactivity. The reduction or loss of mobility induces a deconditioning of the muscular activity which should also be associated in part with an anatomic-functional modification of the peripheral circulation. Above all a modification of the metabolism of the muscles in the state of inactivity is possible. It may, therefore, be postulated that there is a possibility of change in the threshold of reactivity of the arteriolo-capillary system towards metabolites or towards nervous inflows themselves coming from the vasomotor center. It is apparent that it is not possible either to exclude the possible formation of particular metabolites with vasoconstrictive effect besides the probable reduction of vasoactive substances of the bradichine type. One can grasp the importance of a modification in the local metabolism of muscular tissue if one considers the predominant role assumed by local chemical regulation to maintain circulatory homeostases.

A quantitative or possibly qualitative modification of local metabolites may perhaps explain the decrease in the local tonus, especially the venous one, observed by some authors. The local reduction of the temperature because of the reduction of the heat evolved by the inactive muscles should contribute, perhaps in a non-negligible measure, to causing a reduction of the caliber of the arteriole-capillary vessels. On the other hand, the fact that there is a modification, even if only mechanical, of the peripheral circulation, is indicated by the observation of the low circulation flow of the hypokinetic subject, with the reduction consequently of the "vis a tergo", which should certainly contribute in no small measure to the reduction of the venous return to the right side of the heart. But there is more: /334
during immobility, the persistence of a normal metabolic activity of the connective tissue will cause the transformation of the latter from tired tissue to dense tissue with perimuscular and intramuscular infiltration which might induce a mechanical alteration of the local circulation. In conditions of normal activity, the function of the connective tissue is to maintain the connection between the cells and organs in their normal structural relations. The movement tends to

modify these structural relations which are slowed down by the connective tissue which tends to restore them. In this continuous interplay, there is continuous destruction, reconstitution and reorganization of a normal fatigued connective tissue. When there is immobility, the collagen system is no longer slowed down in its evolution and in its structurization which causes excessive connective reaction with formation of dense tissue [29]. It should not be believed that because of this structural modification a long period of immobilization is needed because the latter may start after just one week of inactivity [29]. These mechanical modifications, combined with possible muscular contraction which, as we know, has an ischemic effect by squeezing the vessels, and possible biochemical effects, may contribute in no small way to reducing the aerobic capacity of the hypokinetic subject.

Our finding of a reduction in the maximum pulmonary diffusion capacity is consistent with the impossibility of adequate increase of the circulation flow in hypokinetic patients (Figure 8).

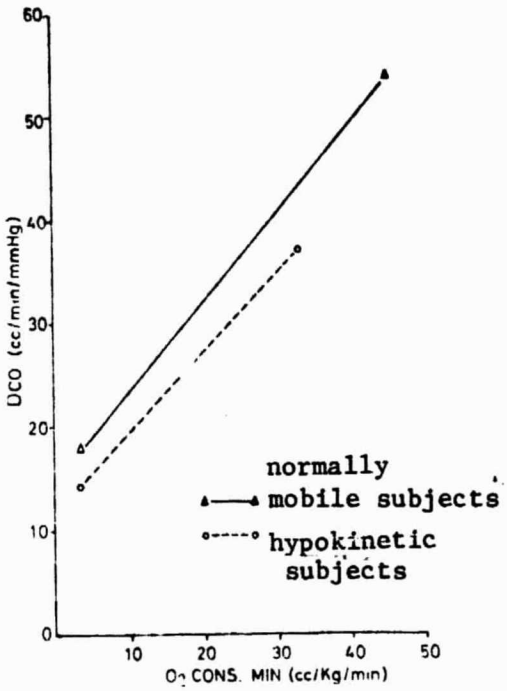

Figure 8

The lower increase of the cardiac capacity may be explained by the same mechanisms discussed in connection with the reduction of circulation flow in conditions of rest. But it should be stated that Saltin et al [8] had noted an equally lower increase of the circulatory flow in muscular work of the same extent carried out by hypokinetic /335 patients both in the supine and orthostatic position. This result made the authors consider the possibility that the lesser increase in the circulation flow is not related exclusively to the reduction of the venous return, but other factors may contribute, such as an altered control of the capacity of the vessels or modifications of the myocardium

itself or both simultaneously. On the other hand, the fact that the reduced cardiac flow is not due exclusively to a reduced venous return because of stagnation in veins of high capacity is proved by the fact that unlike what happens in hypokinetic patients, in subjects with postural hypotension because of changes of venomotor control by damages to the central nervous system, there is return to the normal cardiocirculatory behavior when the subject is placed in a supine position. Another reason for the lack of capacity for adequate circulation flow in physical exercise, at least in the initial phases of muscular work in which a rapid adjustment of the latter is needed, is the reduction of the residual diastolic volume of hypokinetic subjects. The residual cardiac volume, combined with the reserve pulmonary blood, constitutes 30% in subjects in supine position, of the total amount of blood. Now, if it is considered that of these 30%, nearly a quarter belongs to the heart, it can be understood why in the case of a subject incapacitated by a long muscular hypoactivity, the amount of immediately available blood to cover immediate needs induced by work is insufficient. Furthermore, since we know that in the conditions of increase sympathetic tonus there is reduction of the thoracic blood reserve (the opposite of what happens for vagal hypertony), it will be understood how in hypokinesia with adrenergic hyperactivity there may be a decrease in the central blood volume, that is all the thoracic reserve, both cardiac and pulmonary, which plays a vitally important role in the lack of immediate supply of circulation flow for the increased metabolic needs imposed by work.

We have to discuss another well known phenomenon, specifically, the occurrence of orthostatic hypotension in hypokinetic subjects. From the publication by Deitrick et al [3], which may be considered as a classic of the literature on this field, it is noted that in subjects placed in containers from 40 to 50 days, there is poor tolerance to postural variations. It must, however, be stated that in this experiment, in which the subjects were placed in containers, the results /336 cannot be due to immobility alone, but also to the added stress. But considerable reduction of hemodynamic adaptation to the orthostatic condition was observed by Birkhead et al [22] in subjects undergoing bed

rest in supine position for 42 days. Thus, a considerable cardiocirculatory intolerance to postural changes was also observed by Taylor et al [2,14] in their subjects kept in bed and it is worth noting that the orthostatic intolerance is prolonged for a long period after suspension of inactivity as was found by Deitrick et al. It must be emphasized, as apparent from the results of Vallbona et al [30], that 3 days of inactivity in bed are sufficient to cause a cardiovascular deconditioning manifested in considerable increase of the heart rate in passive inclination. Tachycardia and orthostatic hypotension were observed by Graybiel and Clark [31], who were the first to carry out studies on the hemodynamic effects of a prolonged immersion in water. Considerable intolerance to postural tests and to tests of positive acceleration was observed by Graveline's [5] team on Graveline himself, who was immersed in a special tank for 7 days. Graveline and Bernard carried out studies in subjects immersed in water confirming the previous finding of rapid and intense fall of arterial pressure in the actions of passive inclination. In a subsequent study, Graveline [13] observed that postural hypotension did not occur when for the subjects immersed in water, tourniquets were applied to the extremities and inflated periodically. Almost identical results were obtained by Miller et al [10] who determined that the use of all the anti-G reduces the effects of postural changes in subjects who were kept for 2 weeks in bed rest.

As regards the pathogenetic aspect [32], it may be stated that it may be determined by many factors; a reduction of the venomotor tonus, displacements of the circulating mass, etc. These factors may be involved in different ways, with one of them predominating from time to time, also in accordance with the anatomic and functional pre-existing situations. In reality, orthostatic hypotension may also be explained by a more developed adrenergic response in these subjects. An adrenergic response usually causes a considerable shortening of the isometric phase, but with the transition from the clinostatic to the orthostatic position, this is inhibited by a reduction of the ventricular diastolic filling because of a reduced venous return to the right side of the heart. Thus, also, in the usual conditions, the

isotonic phase is shorter with the passage from clinostatic to orthostatic position, still because of the reduced diastolic ventricular filling and because of the liquid column which is a load on the semilunular valves, contributing to the early closing of the valves themselves. Therefore, an increase of the isometric phase, a decrease of of the isotonic phase and especially the shortening of the mechanical systole represents a normal response to postural variations. The object of this reaction is not only to minimize the more difficult venous to the heart, but to increase the myocardiac contractility with shortening of the systolic time and increase of the diastolic time to permit more adequate filling of the ventricle, and thus maintain an adequate cardiac capacity. When there is excessive adrenergic reaction, there is considerable increase of the heart rate which shortens considerably the diastolic period and since the venous return is reduced, there is a decrease in the cardiac flow which thus becomes insufficient. But it must be stressed that there are subjects who after prolonged rest compensate this acrenergic hyperactivity with a vagal action which, through a mechanism of negative feedback control, attempts to compensate for the increased sympathetic response acting as positive feedback. /337

The considerable reduction in the plasma volume observed by many authors after prslonged inactivity, combined with the passage of liquids in the interstitial spaces in the position on the feet, also because of the increase of hydrostatic pressure, favored by venular hypotony, might account for the orthostatic collapse in hypokinetic patients. In this connection, we recall that Deitrick et al and Whedon et al [3-15], observed a considerable increase of the extracellular liquid by measurements of the circumference of the legs in hypokinetic subjects 5 minutes after assuming the orthostatic position. Furthermore, one should not forget the importance of muscular contraction in the acceleration of the transfer of interstitial fluids in the intravascular space because of the increase in tissue pressure. Indeed, the extravascular tissue pressure tends to impede the transfer of liquids outside the vessels. The interplay of transfer of fluids to extravascular spaces may represent a very important factor in the origin of orthostatic hemodynamic changes in hypokinetic subjects. Since the expandable extravascular

space is reduced to the minimum volume during rest it is possible that with the resumption of the orthostatic position, a greater amount of liquid may be transferred in the unity of time to the interstitial tissues, even before the tissue pressure can counteract this rapid transfer. In addition, it was shown that after prolonged inactivity, /338 there is reduction of the venomotor tonus which will, therefore, favor greater stagnation in the peripheral veins. Moreover, we should not forget, as is apparent also from our observations, that many subjects confined to bed for a long time show a disappearance of normal arteriolic response to posture changes (Figure 9). The fact that there subsist in hypokinesia a change in vascular reflectivity is confirmed by the experiments of Miller et al [10] and Whedon et al [15] who observed that periodical intermittent inclinations of patients rendered immobile reduced considerably the hemodynamic intolerance for posture changes. The fact that venous compression, applied intermittently is able to prevent some cardiocirculatory effects resulting from inactivity further emphasizes the importance of the modifications of vascular reflectivity in hypokinesia. Indeed, we must not forget the existence of distension receptors which would also be present in the venous system and whose inactivity would represent a reduction of nervous afferences to the vasomotor centers regulating the cardiocirculatory activity. The elimination of peripheral venous distension because of the want of hydrostatic pressure and the absence of local stimulation caused by the normal flow during muscular activity are certainly factors capable of reducing the venous vasal tonus and the mechanisms of local circulatory adaptation prevailing in the maintenance of normal venous return. There must finally subsist a modification of the pressoreceptor tonus, requiring continuous stimuli like all other activities with reduction of the afferences to the vasomotor center. It must be recalled that Shutz [33] does not hesitate to affirm that the training of an /339 organism to exercise is in many aspects mainly the training of the vasomotor centers. Now it is possible that inactivity should lead to central insufficiency with disruption of the fine regulation tending to maintain circulatory homeostases in the most varied conditions imposed by life. It can also be postulated that the absence of muscular activity includes a type of disruption of the chemoreceptor response. For example,

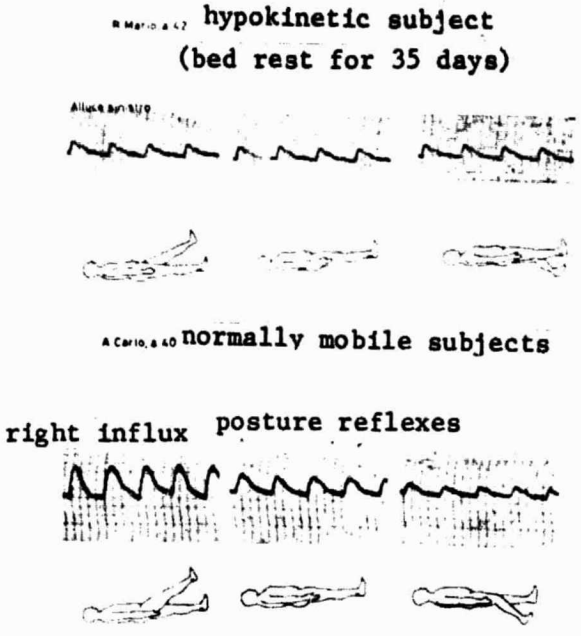

Figure 9

tonic activity of the vasomotor center is regulated continuously by variations in CO_2 concentration, relating mostly to muscular work, whose lack may be the cause of a reduction of the tonic stimulus on the vasomotor center. The central disruption of the chemoreceptor type may also be due and not for the least, to absence of local metabolites normally produced in muscular activity and acting as continuous stimulus adequate for the reflex vasomotor activity.

The duration of the period of isometric tension is also a useful parameter to evaluate the positive inotropic-adrenergic activity and the cholinergic or negative inotropic-inhibitive sympathetic activity on the cardiac activity, independently, from the causal and quantitative viewpoints, of heart rate and peripheral resistances. Using this parameter, it was seen that unlike well trained subjects, in persons with little muscular activity or in a state of inactivity, the isometric phase of the systole is shortened because of prevalent sympathetic hyperactivity [7,9,34].

It was seen that the duration of the isometric systole dropped proportionately to the decrease in the degree of physical activity [9,34]. Therefore, unlike training which causes a cholinergic effect

with consequent extension of the isometric phase, inactivity causes the opposite effect with shortened isometric phase and reduction of the duration of the mechanical systole. The ratio of the duration of the isotonic phase to that of the isometric phase is called hemodynamic ratio and has been found to decrease with the reduction of cardiac capacity [7]. In hypokinesia, we find indeed decrease of the above mentioned ratio as well as a reduction of the cardiac capacity. Vallbona et al [7] noted that the above mentioned ratio tends to decrease progressively with the continuation of the rest. The state of adrenergic hyperactivity during inactivity may be related with an increased release of catecholamine. Indeed, both Graveline [5] and Vallbona [7] observed an increase in the excretion of catecholamine in their hypokinetic subjects unlike the observations of Birkhead et al [35], but the results of the latter may have been distorted by the fact that the collection of the urine specimens were carried out only every 6 days. According to Vallbona et al [7] the release of catecholamine during inactivity may be of an extent such that it does not induce modifications at the arteriole level, but can alter the myocardiac inotropism with shortening of the systolic period. This does not seem likely in the light of our studies which reveal that in the subjects confined to bed for a long time, the peripheral vascular resistances are high and would also be inconsistent with the finding of an increase in the speed of the sphygmic wave observed by the same authors. /340

It was also noted that in hypokinetic subjects training meant a progressive increase of the inhibitor inotropic-sympathetic or cholinergic mechanisms. The effect of training was more apparent in subjects whose sympathetic tonus was higher. It was thus also noted that the elimination of the vagal tonus by means of atropine in hypoactive subjects causes lower adrenergic prevalence in active subjects. This leads to the belief that in hypokinesia the antiadrenergic mechanisms are less powerful in accordance with the concept of a deficiency in such subjects of the cholinergic and/or sympathetic inhibitor mechanisms. We have in support of the fact that during inactivity there is prevalence of the adrenergic type the studies on hemodynamic behavior during the Flack test in subjects before and after a period of inactivity [36]. It was observed that inactivity was able to alter the hemodynamic response during the test. Indeed, we found a higher and persistant overshoot at the end of the action at the time when there was a collapse of

the intrathoracic pressure. This behavior may be the expression of an increased sympathetic response to hemodynamic effects due to the increase of the intrathoracic pressure, for the purpose of compensating the reduced venous return in the phase of forced expiration.

Therefore, the shortening of the mechanical systole, tachycardia, the increase in circulation resistances, the increase of the speed of the sphygmic wave, etc., occurring in hypokinesia are events related to sympathetic hyperactivity and quite the opposite of what happens with muscular training in which cholinergic activity prevails.

Although there are no human anatomic and pathological data proving necrotic and degenerative changes of the myocardiac fibers relating exclusively to inactivity, it is possible that this may happen on the basis of some experimental data and from the theoretical point of view. From the data known to us it seems that the neurohormonal modification at the myocardiac level which includes a biochemical change of the myocardiac fiber with resulting degeneration and necrosis may play a predominant role in the reduced muscular activity. /341

A persistent exaggerated adrenergic activity on the heart, as it is found in muscular inactivity both because of excess formation or accumulation of catecholamine and adequate cholinergic and/or inhibitor sympathetic counterregulation, may cause ischemic damage to the heart with all the consequences relating to it. Indeed, the excess of catecholamine causes a useless overconsumption of oxygen with the possibility of relative myocardiac hypoxia. It is apparent that the functional damage would be greatly increased in the presence, for instance, of a coronary sclerosis which decreases the supply of O_2 or arterial hypertension which increases the need for oxygen on the part of the myocardium. In an extensive anatomical and pathological study on a large number (3,800) autopsies carried out in London, Morris and Crawford [37] were able to observe that in subjects with muscular hypoactivity, the most frequent anatomic-pathological change was represented by myocardial fibrosis, more than coronary athoromasia. It would appear, therefore, that the anatomic-pathological manifestation of the persistent catechol

amine hyperactivity at the myocardiac level is represented by myocardiac fibrosis. Furthermore, it would seem that muscular inactivity acts on the myocardium more by exaggerated consumption of O_2 by the myocardium through disruption in the regulation of the autonomous nervous system controlling the oxidative tissue metabolism than by modifying the coronary circulation. Actually, the adrenergic hyperactivity with catecholamine hyperincretion reduces the percentage conversion of oxidative energy into mechanical work with oxygen dissipation. The increase of vascular resistances, because of the increased need for O_2 by the myocardium, may also be a cofactor in inducing relative hypoxia of the hypokinetic heart.

But it should not be forgotten that the shortening of the diastolic period in hypokinetic subjects with sympathetic hyperactivity may contribute in no small measure to the reduction of the coronary flow, occurring at maximum in this phase of the cardiac cycle. Myocardiac integrity depends on the close relationship existing between oxygen supply on one hand and the neuroregulated myocardial consumption on the other. From the above stated, it would appear that this ratio is deeply altered in a hypokinetic heart. It is clear that if there also exists a coronary sclerosis with altered compensatory vasomotor condition, the excessive O_2 consumption by the myocardium due to the adrenergic hyperactivity in the hypokinetic subject will be even less satis- /342
factory with greater vulnerability of the myocardium. On the contrary, the antiadrenergic action induced by training, which reduces the sympathetic hyperactivity decreases this vulnerability, helping to safeguard the integrity of the myocardiac tissue even in the presence of restriction and vasculocoronary rigidity. The physiopathological modifications of the heart may also be related with a modification of the electrolytic distribution in the cardiac muscle and, in particular, potassium. Bajusz [38] had proved that muscular exercise causes an increase of potassium concentration in the myocardium. On the contrary, the administration of high doses of sympathetic-mimetic amines may cause potassium depletion. Therefore, the hypothesis may be put forward that besides the above mentioned factors related to adrenergic hyperactivity, the functional cardiac damage of subjects with muscular hypoactivity may be promoted by the reduction of the potassium ion in the myocardium, as

noted by Kjellmer [39] which can induce in itself vasodilation in the myocardium and the increase of the vasodilation effect of low hematic pO_2.

It is apparent that the want of physical exercise with the physiopathological changes it causes contributes considerably to the ischematizing factors which with the resulting hypoxia, lead to the degenerative processes of the myocardium.

We hope to have contributed to the knowledge of some aspects of the physiopathology of heart and vessels related to muscular inactivity, but, on the other hand, considerable further studies must be carried out to be able to elucidate better the pathogenetic mechanisms of the cardiocirculatory functional damages due to hypokinesia such as: 1. mechanism of orthostatic hypotension with the related phenomena of reflexogenic hyporeactivity; 2. the intimate mechanism by which the circulation flow is reduced; 3. the mechanism concerning the modifications of the peripheral vascular resistances; 4. the behavior of the arteriole-capillary peripheral circulation at the muscular level and the local metabolic changes in the muscle with possible release of pathological reflexes; 5. the behavior of the hemodynamics of the minor circuit still totally unknown; 6. the effects of rest should be quantized on a larger variety of subjects, healthy and of different age, physical training, occupation and physiological conditions; 7. it is also important to determine the role played by the neuroendocrine system and in particular the hypothalamic-pituitary-suprarenal system, /343 whose functional variation may be one of the basic causes of the changes in the cardiovascular system during inactivity.

A deeper knowledge of the physiopathological and clinical aspects of the hypokinesia and in particular the relationships between muscular inactivity and the anatomic and physiological aspects of the cardiovascular system are, therefore, needed for a better understanding of the problem. This appears to us as particularly important if we consider also that in the western civilization the hypokinetic person represents the most frequently occurring type as compared with the minority of

physically trained persons who represent a modest fraction of subjects with a positive deviation from the normal standard of the western nations. Furthermore, a deeper study of the cardiovascular neurovegetative aspects induced by muscular inactivity and more extensive knowledge on the part of the practicing doctor, of the anatomic and functional damage resulting from hypokinesia will lead directly to a more systematic and rational use of physical exercise as both therapeutic and prophylactic means for degenerative cardiovascular diseases.

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