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Invited Address - The Possible Role of the Coronary Flow in Determining Myocardial Oxygen Consumption

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The Possible Role of the Coronary Flow in Determining Myocardial Oxygen Consumption[1]

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When Dr. Thielen first contacted me in connection with this talk, I thought I would discuss some factors that influence the strength of contraction of heart muscle, including human heart muscle. (By including data from humans I felt I could stay within the framework of the general topic of today's seminar.)

However, since that time I have been writing a paper on some of my work with isolated strips of heart muscle. This work concerns the relation of the oxygen consumption of the heart to the strength of its contraction, the frequency at which contraction occurs (the heart rate), and the length of the muscle. Out of the reflections over these results has come what is, to my knowledge, an original concept concerning the energy turnover in heart muscle. I would like to show you the path I took in arriving at the tentative conclusion put forth here regarding the relation of the oxygen consumption of the heart and the blood flow through the heart muscle.

As most of you are well aware, biological research can range from the study of a single enzyme with one source of energy to the study of intact man, or even thousands of men. There are advantages and disadvantages at every level of complexity. Valuable knowledge accrues all along the line. To mention only one positive benefit from the isolated studies, cooling of the heart during surgery was instituted on the basis of earlier knowledge concerning the effect of cold on chemical reactions. On the other hand, extrapolating the knowledge gained from isolated systems can often be dangerous. For example, one of the oldest concepts in physiology, based on results from the isolated heart, and called "Starling's *Law* of the Heart," is now in jeopardy as a result of recent experimentation on intact animals and man.

In our studies we have chosen a compromise between extreme isolation and the complete organism. We have used small strips of heart muscle from rats, cats and humans. Our studies on the human

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strips are incomplete, but as far as we have gone the human in most respects appears to resemble the cat.

You may ask why we chose the isolated heart strip. We wanted to assess the influence on the oxygen consumption of variations in frequency (or heart beat); length, or stretch (comparable to filling of the heart); tension (or force of contraction); and the effects of work, e. g., pumping blood. In an intact heart, what is a distinct advantage to all of us here, namely, a spontaneous beat, was a disadvantage for our work. We had to be able to control the frequency of contraction precisely. Therefore we preferred to have the heart strip quiescent, and stimulate it electrically, which causes no harm to the tissue. Also, since the intact heart is continually changing in size to meet the demands of the circulation, it is difficult to determine the exact length of the heart muscle. To mention one more parameter, the blood flow to the heart muscle cells usually varies considerably, in quantity and composition; oftentimes changing spontaneously. We needed to know that the availability of oxygen and nourishment would be the same at all times throughout the experiment.

After three years of mostly discouraging and sometimes ludicrous efforts, a technique was devised and perfected which was found to be adequate for the study. Many persons have contributed to its development. We can change the length of the muscle and the frequency of the contraction. We can permit the muscle to shorten and lift a weight, thus doing external work, or we can prevent its shortening and prevent external work. Oxygen consumption is measured simultaneously, while the environment in which the muscle is placed remains constant.

As implied earlier, in an isolated biological system there is always the question of whether the preparation is "normal" or not. Is the performance of the strip typical of the heart *in situ* (in the body)? The objections usually center around the adequacy of oxygen and nutrients so necessary for mammalian metabolism. Since there is no blood supply, oxygen and nutrients must pass into the tissue from the outside of the muscle. To reduce the problem caused by the relatively slow diffusion into the muscle, only small, thin muscles have been used. These muscles will continue to contract for two to three days; the oxygen consumption remains relatively constant, and is of the same order of magnitude as that measurd in the blood-perfused whole heart, i.e., hearts which are nourished with whole blood by the coronary arteries, their normal source of supply.

Summarizing our results using this technique, we found that there was a small but significant increase in oxygen consumption as the muscle was stretched. The force of the contractions, i.e., the devel-

oped tension, appeared to be of little significance as far as the oxygen consumption was concerned. On the other hand, increasing the heart rate from 60 to 120 beats per minute doubled the consumption of oxygen. Finally, we observed that under most conditions the oxygen consumption was actually depressed if the muscle lifted a weight, i.e., if it performed work.

These results came as something of surprise since most of them were contrary to expectations based on studies in the intact heart. Muscle length, or in other words, heart size, has long been emphasized as a major determinant of energy liberation. Yet we found only a small increase in oxygen consumption as length was increased. The effect of the increase in heart rate was not so unexpected; in fact the increase in oxygen consumption is about the same as that measured in the intact heart. As for the effect of work, some recent studies on the intact heart tend to show that work plays a minor role, although not a negative one as we have often found. The matter of the effect of tension has of late come into prominence as the major factor which determines oxygen consumption. This view is the most controversial, and in comparison with our studies, the most divergent. In the intact heart the tension developed by the heart in expelling blood correlates extremely well with the oxygen consumption; when tension rises more oxygen is taken up by the heart, and vice versa. Therefore, the maintenance of tension has been blamed for the vastly increased oxygen consumption seen when the heart pumps blood against a high pressure in the aortic artery. Yet we found no significant effect of tension on the oxygen consumption. How might these discrepant results be reconciled?

It happens that tension (or force of contraction) is a function of the pressure in the aortic artery and in turn aortic pressure is the major determinant of the coronary blood flow supplying the heart. Finally, it has been found that coronary blood flow and oxygen consumption rise and fall together. As a result of this latter relationship, it has generally been concluded that the blood flow to the heart is regulated by the oxygen demand. Thus, it reasoned, if the heart uses more oxygen as a result of pumping blood against a high pressure, the coronary flow increases to take care of the need.

Recently, I have come to the conclusion that this reasoning may be in error. It may be that we have been misled by preconceived opinions. It has been said that because the influx of Presbyterian ministers exactly paralleled the rise in the whiskey consumption in Africa, Presbyterian ministers must be heavy drinkers and their influx must have been the cause of the increased whiskey consumption. Now, you don't believe this, I'm sure, but what if there had been an influx of British sailors? Now, there would be no doubt in the minds of many regarding the causation.

In the same way one might reason that if work is performed or tension developed, the energy must come from somewhere, and that would be a correct assumption unless our laws of thermodynamics are wrong; and all the evidence indicates that they are not. But the laws of thermodynamics do not demand that the pathway for energy liberation must always be the same. In other words, at times heat alone is liberated during a reaction, and at other times much of the energy is turned into work.

Now, let us consider the oxygen consumption, or, in other words, the energy liberation of the heart. I offer an alternative explanation for the large increase in oxygen consumption seen when the tension increases in the intact heart. I suggest that the correlation might be a spurious one arising from the fact that when tension rises, coronary blood flow increases due to the concomitant rise in aortic pressure, as mentioned earlier; *and* that it is the increase in coronary blood flow which increases the oxygen consumption, rather than that the coronary flow is somehow adjusted to the oxygen demand.

This tentative hypothesis would explain the discrepancy between our results on the isolated strip where the oxygen and nutrient supply remain constant and the results from the intact heart with its variable coronary flow. There are some additional pieces of evidence which point in the same direction. To mention one, it has been found by others that if coronary flow was increased in the intact heart, while maintaining tension and other factors constant, the oxygen consumption increased markedly.

In terms of the energy exchange this hypothesis means that the heart continually burns oxygen which is ordinarily degraded into heat unless called upon to do work. This wasteful oxygen consumption is ordinarily limited by the oxygen availability. We have been taught that the heart cannot contract an oxygen debt. Could it not be that it is always in "relative" debt?

Let us consider an analogy. Imagine a lazy woman of "the twenties" whom we might call "Sweetheart", reclining on a couch eating chocolates, for which she has a voracious appetite. We assume that Sweetheart also has a high metabolic rate and can burn all the candy that is brought to her by her servant, Coroni. Whether she does any work (or develops tension) is not related to her intake of chocolates but rather to the ire of her husband. On the other hand, Sweetheart's intake of chocolates is largely determined by the diligence of the servant who keeps her supplied with the candy. Obviously, she and the servant as well are burning energy to serve no useful purpose—an inefficient arrangement at best. There are some sophistications which might be applied to modify this simple

analogy, but in general it may represent the true picture.

What are the implications of the suggestion that the oxygen availability is one of the major determinants of oxygen consumption, in addition to initial length of the muscle and the frequency of the contractions? Much current research has been directed at finding ways to increase the coronary flow. If the view presented here is correct, this may be wasteful approach, although, obviously, at times it is necessary to increase coronary flow. Is it perhaps comparable to hiring another servant to bring more chocolates to our heroine so that she can burn more energy? Would it not be preferable to have a half-time servant and treat our slothful woman with psychotherapy with the view toward reducing her craving for chocolates and at least increase the efficiency of doing what little work she does do? This therapy for the heart might consist of an attempt to cut down on the appetite of the heart for oxygen, perhaps by means of a selective metabolic inhibitor. This would be most practicable if the energy for the resting, or "maintenance", oxygen consumption can be separated from the activity oxygen consumption, for which idea there is some slight evidence.

Is it not possible that we already are using such metabolic inhibitors without realizing their true role? As one example, nitroglycerin relieves the pain of angina pectoris (pain caused by coronary artery disease). Now nitroglycerin is presumed to be helpful because it increases coronary blood flow, yet nitroglycerin in the studies of which I am aware did not increase coronary blood flow. Could this be metabolic therapy?

I offer this view of the regulation of the oxygen consumption of the heart only as a suggestion. Many of my colleagues will disagree, but there seems to be enough evidence to warrant serious consideration.