The Interpretation of "Spurious" Correlations in Coronary Flow Literature

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Coefficients of correlation between coronary sinus blood flow and several cardiac variables have been analyzed from data obtained by the nitrous oxide desaturation method in dogs. The $r$ value for flow and left ventricular oxygen consumption is an example of the correlation of two variables having a common element. The high values reported in the literature for this relationship may also be obtained with numbers drawn at random. Accordingly such values should not be accepted as valid evidence of a functional relationship between coronary blood flow and myocardial oxygen consumption.

A high positive correlation, between flow and heart rate in the normal dogs and a significant inverse correlation between flow and arteriovenous oxygen difference in the chronic sympathectomized dogs, was observed.

A high coefficient of correlation between coronary blood flow and calculated left ventricular oxygen consumption has been reported in several recent papers, and this has apparently been accepted as valid evidence of a functional relationship between the two variables. Although such a functional relationship may exist, evidence of this kind, whether expressed as an $r$ value or plotted graphically, can not be accepted on statistical grounds alone.

This report analyzes the evidence on this point and is based on data taken from a previous publication of coronary blood flow studies obtained with the nitrous oxide desaturation method. A discussion of several other correlations of physiologic importance is included.

Results

Table 1 lists the coefficients of correlation between coronary blood flow and several variables, and the corresponding $p$ value in each case. The original data upon which these statistics are based may be found in the preceding publication in which the column numbers, type of anesthesia, experimental procedure, etc., are tabulated in the same manner. There are also listed (column 11) $r$ values for random numbers and an evaluation of a comparison with the experimental values of column 8. Before interpreting this data the significant $r$ values for each variable may be noted.

Left Ventricular Oxygen Consumption. The $r$ value is uniformly high in all categories including the random numbers.

Coronary Vascular Resistance. A uniformly high inverse $r$ value is present in all categories including random numbers.

Coronary Arteriovenous Oxygen Difference. A high $r$ value of probable statistical significance occurs with chronic sympathectomy only.

Mean Arterial Pressure. A high $r$ value occurs only with chloralose anesthesia.

Left Ventricular Work. A high $r$ value is present with chloralose anesthesia only.

Heart Rate. Probably significant values are present with Dial-Urethane (diallylbarbituric acid and urethane) anesthesia and with Dial-Urethane plus atropine.

Discussion

Perhaps the most prominent feature of the tabulated $r$ values is the uniformly high values for left ventricular oxygen consumption and for coronary vascular resistance in all categories, including the random numbers. If the correlation between coronary blood flow (CBF) and arteriovenous oxygen difference ($A-V O_2$) is designated $r_{xy}$, where $x =$ coronary blood flow and $y = A-V O_2$, then the cor-
TABLE 1.—Evaluation of Coefficients of Correlation (All Correlations are with Coronary Flow)*

<table>
<thead>
<tr>
<th>No. of cases</th>
<th>Cor. A-V O₂</th>
<th>Cor. LV O₂ cons.</th>
<th>MABP</th>
<th>CVR</th>
<th>Heart rate</th>
<th>LV work</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cor. r</td>
<td>p</td>
<td>Cor. r</td>
<td>p</td>
<td>Cor. r</td>
<td>p</td>
</tr>
<tr>
<td>10</td>
<td>0.203</td>
<td>0.06</td>
<td>0.897</td>
<td>0.005</td>
<td>0.049</td>
<td>0.04</td>
</tr>
<tr>
<td>10</td>
<td>-0.269</td>
<td>0.40</td>
<td>0.874</td>
<td>&lt;0.0001</td>
<td>0.005</td>
<td>0.0004</td>
</tr>
<tr>
<td>12</td>
<td>0.043</td>
<td>&gt;0.6</td>
<td>0.715</td>
<td>&lt;0.0001</td>
<td>0.018</td>
<td>0.092</td>
</tr>
<tr>
<td>10</td>
<td>0.191</td>
<td>&gt;0.6</td>
<td>0.697</td>
<td>&lt;0.0001</td>
<td>0.072</td>
<td>0.45</td>
</tr>
<tr>
<td>25</td>
<td>0.092</td>
<td>0.4</td>
<td>0.874</td>
<td>&gt;0.0001</td>
<td>0.030</td>
<td>0.5</td>
</tr>
<tr>
<td>25</td>
<td>0.004</td>
<td>&gt;0.6</td>
<td>0.715</td>
<td>&lt;0.0001</td>
<td>0.018</td>
<td>0.092</td>
</tr>
</tbody>
</table>

*Cor. = coefficient of correlation of coronary flow with indicated variable. p = probability of value being due to chance. Atrop. = atropine sulfate. Acute B. vag. = acute bilateral cervical vagotomy. Chronic sympa. = chronic sympathectomy. A-V O₂ = coronary arteriovenous oxygen difference. LV O₂ cons. = left ventricular oxygen consumption. MABP = mean arterial blood pressure. CVR = coronary vascular resistance. Column 10 represents experiments in which a gas mixture of 21 per cent oxygen, 15 per cent nitrous oxide in nitrogen was used. In all other instances a mixture of 15 to 20 per cent nitrous oxide in oxygen was used.

The relation between coronary blood flow and ventricular oxygen consumption may be designated \( r_{x,y} \). This is true because the oxygen consumption is calculated by multiplying CBF and A-V O₂.

The correlation of a variable with the product of it and another variable or with the quotient of two variables is called correlation involving common elements, and were termed "spurious" correlations by Karl Pearson. As pointed out by Snedecor, the interpretation constitutes the spurious feature. As a means of evaluating the \( r \) for left ventricular oxygen consumption, the calculations were repeated with random numbers drawn from tables of random sampling numbers, after these numbers had been adjusted to the same mean and variance as the experimental data of column 8. It will be noted from the table that the random number \( r \) values for A-V O₂ and for left ventricular oxygen are similar to the experimental data. Comparing them specifically to the data of column 8 we see that the latter values fall within the confidence interval at the 95 per cent level for the random numbers and do not have a statistically significant difference from the random numbers.

The correlation of coronary blood flow with resistance (CVR) presents the same problem as discussed above. Here \( r_{x,y} \) equals the \( r \) for flow and mean blood pressure (MABP), and the correlation of flow (CBF) with resistance equals \( r_{x,y} \) because CVR = MABP/CBF.

The similarity in \( r \) values, confidence intervals, and significant differences are very close to those for flow and left ventricular oxygen consumption in relation to the random numbers.
It should be pointed out that a constant value for A-V $O_2$ and a variable CBF will give an $r_{xy}$ of zero but an $r_{xy}$ approaching unity. This is typical of the values listed in the table.

Since the $r$ values of numbers chosen at random are similar to those for flow with oxygen consumption or flow with resistance it would appear that such values may be obtained by multiplication and division and do not necessarily indicate a significant correlation between the physiologic variables in question. The point has been discussed at some length because of the frequency with which correlation of this kind are misinterpreted in the literature. Several papers have attached physiologic significance to a high correlation between coronary blood flow and calculated oxygen consumption.\(^1\)\(^-\)\(^4\) Allela et al.,\(^6\) on the basis of statistical analysis, state that "oxygen consumption appears to be the most important factor determining coronary flow." Fultz et al.,\(^1\) using the same experimental method, have published $r$ values quite similar to ours, and a current standard text book of physiology has stressed the significance of their high $r$ values in interpreting the role of oxygen metabolism in the regulation of coronary blood flow. Such a correlation may well exist but statistical analysis of the type described can not be accepted as valid support for this.

Other examples of correlations involving common elements have appeared in two articles.\(^5\)\(^,\)\(^9\) An $r$ value of $-0.89$ has been reported for the arterial oxygen content ($\Delta O_2$) and the coefficient of oxygen utilization ($\Delta O_2 - V O_2$) under conditions of hypoxia. It should be clear that the physiologic significance of this value must be critically evaluated since a variable (arterial oxygen) is correlated with a ratio in which the arterial oxygen appears in both the numerator and the denominator, i.e.

$$\frac{\Delta O_2}{\Delta O_2 - V O_2}$$

In addition to the analysis of spurious $r$ values obtained from the data of table 1, several relationships of physiologic importance may be noted. With one exception the $r$ value for coronary blood flow and A-V $O_2$ in the several categories is low, and statistically is not significant. Apparently this is due to the fact that the A-V $O_2$ remains nearly constant under these experimental conditions. The exception is the data with chronic sympathectomized animals where there is a statistically significant inverse correlation between flow and A-V $O_2$. The value $-0.79$ is remarkably high for a small sample of 10 cases. This group is characterized by a low coronary blood flow, ventricular oxygen consumption, and heart rate, but by a high ventricular efficiency. The group was classified in the previous paper\(^8\) as class 1(e),\(^-\)\(^-\)\(^1\), in which oxygen consumption was reduced relatively more than coronary blood flow when compared to the normal series. The high inverse correlation between flow and A-V $O_2$ appears to be due to the fact that removal of the sympathetic innervation of the heart not only reduced the cardiac oxygen consumption but also made it quite constant relative to coronary blood flow. Support for this interpretation is found in the fact that the standard deviation for left ventricular oxygen consumption in this group is smaller than in any of the other experimental situations.

It is surprising to find a low correlation between flow and mean arterial blood pressure in most of the categories. Only in the normal group with chloralose anesthesia (column 8) was the $r$ value highly significant. No explanation at present is available. The high $r$ for flow and ventricular work in the same group is dependent upon the blood pressure, since the work estimate is calculated from the former value.

The correlation between flow and heart rate also is low in most of the categories. The influence of heart rate upon coronary flow has been the subject of much conflicting opinion. The mechanical effects of increasing rate probably tend to reduce flow by increasing the systole: cycle ratio of duration of systole to that of the entire cycle. However, this effect may be reversed as a result of the dilatation associated with the increased metabolism. The $r$ value for the average flow and the average
heart rate in each of the 10 columns shown in table 1 of the previous paper is 0.91. Thus a high correlation of flow with heart rate persists with average values in spite of the variation in anesthesias, cardiac innervation, use of atropine, etc.

**Summary**

A study of the coefficient of correlation of coronary blood flow with several cardiac variables has been presented. Correlations of variables in the field of circulation in general, and the heart in particular, frequently involve two variables having a common element. The common element appears to be responsible for the relatively high r values obtained, as indicated by the very similar results obtained with the use of random numbers. This invalidates r values of this type as evidence of a functional relationship between the two variables in question. The above argument applies to the r for flow and calculated myocardial oxygen consumption and for flow and calculated coronary resistance.

The data also include the correlation of flow with other cardiac variables which do not have a common element. The high inverse r value for flow and the coronary A-V O2 in chronic sympathectomized animals is apparently due to a reduced and relatively constant myocardial oxygen consumption in such preparations. A high correlation between coronary blood flow and heart rate persists with a variety of experimental conditions.

**SUMMARIO IN INTERLINGUA**

Es presentate un studio del correlation inter le fluxo de sanguine coronari e plure alte variabiles cardiac. Correlationes de variabiles in le campo del circulation in general—e del circulation cardiac in particular—es frequentemente concernite con pares de variabiles que ha un elemento commun. Iste presentia de un elemento commun es apparentemente responsabile pro le relativemente alte valores de r que es obtenite. Un corroboration pro isto es a vider in le facto que multo simile resultatos es obtenite per le uso de cifras casual. Isto rende invalide valores de r de iste typo como indication de un relation functional inter le duo variabiles in question. Le supra-presen-
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