Incomplete Cryoactivation of Human Renin: A Cause of Confusion?

To the Editor: Matsunaga and colleagues recently reported in Hypertension the reactivation of inactive renin in normal human plasma. Their study included the use of activation by acidification, trypsin, kallikrein, and cold exposure. Optimal conditions for acid, trypsin, and kallikrein activation of human renin appear to have been agreed upon, but doubt remains as to the ideal duration and temperature for maximal cryoactivation. Periods at −4°C of as short as 48 hours or as long as 90 days have been employed.

It is noticeable from the data of Matsunaga and colleagues (who used a period of 7 days at −4°C for cryoactivation) that no plateau of renin activity is demonstrated, and that there appear to be significant increases in renin between Days 6 and 7. We have recently described continuing cryoactivation for between 15 and 24 days at −4°C; Pietro et al. have also suggested that the process may take 15 days at −5°C for completion and be biphasic, while Hummerich and colleagues have reported increases in renin concentration continuing for as long as 3 months at −5°C.

Our results showing the time course of cryoactivation of renin in serum from 11 healthy ambulant normotensive subjects are presented in figure 1. At Day 6, 62.8% ± 7.1% (mean ± SD) of the eventual 36-day activation had occurred and by Day 10, 77.9% ± 7.3%. These figures suggest that, under the conditions described, only 65% to 70% of "cryoactivatable" renin was in fact so activated in Matsunaga’s studies.

In our healthy subjects, a mean of 80.3% of total renin activity was in the cryoactivatable form (range, 73% to 94%).

It thus appears likely that, in their recent study, cryoactivation was incomplete, which makes comparison with other methods of activation and interpretation difficult if not impossible. With the variety of different methods in use and the recently added complexity of reinactivation, there are clearly considerable possibilities for confusion. It would appear vital that all such studies should include clear evidence of completion of activation with each technique used.

References

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Author’s Response:
I have no objection to Drury’s opinion that the cryoactivation of plasma inactive renin is incomplete in 7 days at −4°C. And if, for example, one intended to compare the efficacy of cryoactivation at this point with that of other activation procedures, there would be confusion. However, the purpose of our study was to show the existence of two different mechanisms of cryoactivation, reversible and irreversible. The latter is plasma kallikrein-dependent and the former is not. The reversible cryoactivation was obtained in the presence of soybean trypsin inhibitor. It reached a plateau within 5 days, with no more significant increase in renin activity up to the 14th day, while the cryoactivation under the conventional condition was still continuing. This relation can be seen in figures 3 and 4 in our paper. That is why we considered that 7-day cryoactivation was enough for our purposes and did not result
in any confusion in our conclusion. The biphasic nature of cryoactivation at \(-5^\circ\text{C}\) observed by Pietro et al.\(^1\) may represent the phases of cryoactivation before and after the activation of plasma kallikrein. In our study under the conventional condition, the activation of renin at \(-4^\circ\text{C}\) preceded and seemed to be accelerated after the activation of plasma kallikrein, which took a few days before the initiation.

References

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Strange Companionship
To The Editor:

One of the unnecessary and useless recommendations made by the World Health Organization was to introduce the units of the Système International (SI units) into medicine. Among the numerous unfortunate consequences of that red-tape decision, there was the suggestion to use kilo Pascal (kPa) instead of millimeters of mercury (mm Hg) as the unit for measuring blood pressure. For those who do not know what kPa means, the definition should be stated as follows: the basic unit for pressure in newton per square meter is the Pascal (Pa); 1 mm Hg column equals 133.322 Pa or 0.133 322 kilopascal (kPa).

Use of the kPa as the unit for expressing blood pressure does not contribute at all to either a more reliable or a more precise measurement, but has the great disadvantage that pressure has to be expressed as a decimal fraction. Thus, a blood pressure of 120/80 mm Hg reads 16.0/10.6 kPa. From a physical point of view, the use of kPa is nonsense, because this 'SI' unit is the abstraction of units to measure pressure.

The American Heart Association was very wise in not accepting the kPa as the unit for expressing blood pressure and in raising general doubts with respect to the usefulness of SI units in medicine. In the "Recommendations for Human Blood-Pressure Determination by Sphygmomanometers" (1981), the AHA stated: "Despite the logic of the SI System it has not been widely accepted in this country." In Appendix 2, the AHA mentioned: "Several South African Nations and West Germany now plan to express pressure in SI units," and in the same paragraph: "One mm Hg equals 1.33 mbar (millibar). Hence, 1 mbar is 1 hPa (hectopascal). This nomenclature is to be used by the Federal Republic of Germany when they employ the SI system."

Fortunately, these statements are incorrect. It is true that the Federal Republic of Germany, following the recommendation of WHO, accepted the kPa as the unit for measuring blood pressure, but the ministry responsible for gauging standards (strangely enough, being part of the ministry of economics) had agreed to use mm Hg as unit besides kPa until 1985. Similar regulations had been issued in the German Democratic Republic, in Austria, and in Switzerland but not, to the best of my knowledge, in the Federal Republic of South Africa.

For several years, the International Society of Hypertension and various national leagues against high blood pressure have tried very hard to convince national and international bodies to renounce the change of the unit for measuring blood pressure and retain mm Hg. These efforts were eventually successful, since the 34th World Health Assembly, on May 22, 1981, decided as follows:

The Thirty-fourth World Health Assembly, Having considered the international difficulties being encountered in attempting to introduce the kilopascal, the unit of the Système International d'Unités (SI) for the measurement of blood pressure;

Noting the attitudes and resolutions of international scientific bodies objecting to the precipitate replacement of the millimetre of mercury by the kilopascal;

Further noting with concern the ensuing difficulties encountered in communication between the scientific community and the population in a number of Member States;

Mindful, nevertheless, of the desirability of a unified international system of units as expressed in earlier resolutions;

Considering the high prevalence of hypertension, its deleterious effect, and the high probability for its prevention by early screening;

Recalling the caution expressed in resolution WHA 29.65 and WHA 30.39 regarding the difficulties that might arise through the precipitate introduction into medical practice of certain units of the SI, with particular reference to the substitution of the kilopascal for the millimetre of mercury in the measurement of blood pressure;

1. CONSIDERS that there is no compelling need to replace the millimetre of mercury by the kilopascal in medical practice at the present time;
2. RECOMMENDS that the millimetre of mercury and the kilopascal be used simultaneously until a future World Health Assembly considers the retention of the millimetre of mercury unnecessary for the undisturbed delivery of health care and the interchange of scientific information; and,
3. REQUESTS the Director-General to draw attention to the present resolution in the Organization's journals as well as through the media of the relevant nongovernmental organizations."

The language of international organizations such as WHO is full of clauses, but the long-winded text
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