REVISTA ESPAÑOLA DE FISIOLOGIA, 48 (4), 239-244, 1992

Analysis by Digital Simulation of the Peripheral and Renal Resistance in Hypovolemic Hypotension

L. Roa*, F. Garrachón and S. González-Barón*****

Grupo de Ingeniería Biomédica
Escuela Técnica Superior de Ingenieros Industriales
41012 Sevilla (Spain)

L. ROA, F. GARRACHÓN and S. GONZÁLEZ-BARÓN. *Analysis by Digital Simulation of the Peripheral and Renal Resistance in Hypovolemic Hypotension.* Rev. esp. Fisiol., 48 (4), 239-244, 1992.

A haemorrhage was simulated and analysis of dynamic behaviour of renal resistance, renal nervous activity and peripheral resistances were processed, with the aim of studying the paradoxical behaviour of renal resistance as opposed to peripheral resistances and the increase of sympathetic activity in hypovolemic shock situations using both non-linear models of the renal blood flow and arterial pressure and body fluids. The following conclusions can be made after comparing the results obtained by simulation with data related to animal experimentation models: the model is useful for its use in the analysis of nervous activity, resistance and renal flow in hypovolemic shock situations in humans and the control structure it puts forward can explain the paradoxical behaviour of renal vascular resistance as opposed to the peripheral resistances and the increase in the renal nervous activity in the aforementioned circumstances.

Key words: Renal vascular resistance, Renal nervous activity, Hypovolemic shock, Modelling and simulation.

The adjustments in resistance to the blood flow in tissues during hypovolemic hypotension are directed to a redistribution of the blood supply which allows an adequate oxygenation of the vital organs (brain and heart), even at the expense of the ischemia of other organs (skin, muscle, gut, etc.). A priority in the maintenance of the flow could be established, in such a way that the kidney would be in an intermediate position between both extremes.

The different regulation mechanisms of the flow proposed to explain this behaviour includes intrinsic properties of the vessels and others, derived from the neural action upon them. Most authors accept that the intrinsic mechanisms are the prime ones for the renal blood flow (RBF)

* To whom all correspondence should be addressed
** Servicio de Medicina Interna, Hospital San Juan de Dios, Sevilla (Spain).
*** Departamento de Fisiología, Universidad de Málaga (Spain).

autoregulation; the nervous system has litle relevance (2). However, under certain circumstances —hypovolemia, hypotension, experimental renal failure— sympathetic renal activity seems to have greater importance, to the extent that it could be the determinant of the differential behaviour of the renal flow against the peripheral flow (5). But, in some cases, this mechanism could give origin to deleterious consequences which are derived from the tissular ischemia. Regarding the kidney, the prerenal acute renal failure, denominated by BADR and ICHIKAWA as a shift of the kidney regulation systems (1), the renal parenchimal failure (tubular necrosis), and, to a certain extent, cortical necrosis, can be complications of hypovolemic hypotension. The frequency and clinical importance of these situations make the study of the physiological mechanisms extremely interesting.

The present work is an application of a mathematical model of the RBF which was previously developed and validated. It expounds how the proposed structure in the model can explain the behaviour of the RBF against hypotension provoked by hypovolemia which was observed in clinic and in animal experimentation.

Materials and Methods

The processes for the development of a model for the study of physiological control systems, according to our groups techniques are as follows: 1) Definition of the goals of the model, 2) Construction of the physiological structure, 3) Quantifications of the proposed relationships (Mathematical model), 4) Codification, 5) Sensitivity analysis, 6) Validation, and 7) Operation (prediction and/or control).

Two different subsystems have been considered: a) A control structure of the RBF and b) a model for the body fluid control.

RBF control structure. — The goal of this submodel is the study of the neural component of the RBF regulation.

Physiological structure: It was considered that the renal vascular tree is a tube system through which a flow passes. This flow is generated by a pressure gradient and the property of the renal system resistance is opposed to it.

The following asumptions —which are common to most of macroscopic hemodynamics mathematical models, had to be carried out to simplify the mathematical model without making it unreal, i.e., resembling the physiological reality as much as possible:

—All the blood coming into the kidney is supplied through the renal artery and all the blood which leaves the kidney does so through the renal vein; for practical aspects the input pressure can be considered equal to the pressure in the aorta and the output pressure to that of the right atrium.

—The input volume (arterial flow) is equal to the output volume (venous flow), plus the urine volume, without any other losses.

—The blood flow is laminar and continuous.

—The fluids are incompressible.

—Inertial terms are not considered.

From what has been previously considered, and as it has been considered a fluids system —with a flow passing through a tube and a pressure gradient causing the flow's movement— there must exist a resistance function (Γ_R), which relates to pressure gradient and flow:

$$\Delta P = \Gamma_R (Q)$$

with ΔP being the difference between the input and output of the system, Q the flow, and Γ_R the resistance function.

In a physiological sense, Γ_R represents the resistance of the vasa implied in the regulation of the renal blood flow.

The development of this resistance function has been previously published (9,

12). A double regulation mechanism of the RBF is proposed: first, an intrinsic renal mechanism, whose physiological basis would be the humoral response, myogenic of whatever other nature, capable of detecting changes in the RBF and varying the renal vascular resistance to keep the RBF constant; the present work does not aim to study this mechanism. The second system is of a neural nature which includes the renal nervous activity, sympathetic activity, a central tonic inhibitor system and a flow-dependent modulator intrarenal system.

The quantifications, codification, sensitivity analysis and validation of the submodel have been previously published (9, 12).

Body fluids control model. — This model is currently in an operational phase, and it has demonstrated to be useful in clinical situations (10-13). In brief, it is a three-compartment model (intravascular, interstitial and intracellular spaces) in which the following regulation system among others were included: short-term regulation of arterial pressure by means of the central nervous system and baroreceptors, medium range regulation through circulatory adaptation and long range regulation by means of the renal system and long range of cardiac output through metabolic needs. The state variables included in the model are total solved substances and volumes. Therefore, conservation of mass is the physics law on which the model is based.

Simulation. — A haemorrhage was simulated in two sections of different velocities: In the first section (from 10 min to 18 min) there is a 150 ml/min blood loss. In the second section (from min 19 to min 25) the haemorrhage velocity is 63 ml/min. The total loss is 1641 ml in 15 min. This simulation was designed to obtain arterial pressure conditions similar to those reported by KOYAMA *et al.* in animal experimentation (6).

The observed variables are: mean arterial pressure (MAP), renal nervous activity (RNA), total renal resistance (RTR), resistance derived from RNA (NR), momentaneous total peripheral resistance (MTPR), and renal blood flow. The basal values for these variables were considered: MAP = 99.5 mmHg, RTR = 92.5 mmHg/l · min, RNA = 0.73 impulse/min, NR = 3.3 mmHg/l · min, MTPR = 19.9 mmHg/l · min, RBF = 1.077 l/min. The results obtained by means of simulation were compared with those mentioned in the bibliography.

Three other simulations were carried out using the same conditions. The following three points were considered: that MAP would vary freely as proposed in the model which was used; that the MAP remains constant because the vasodilation originated by the autoregulation mechanisms could be completely compensated by the vasoconstriction caused by the increase in renal nervous activity; and that the intrinsic renal resistance remains constant, the RTR varying as much as the NR. The validation has been performed by comparing RBF data obtained by simulation with those reported in the bibliography.

Results

After 8 minutes the MAP drops from its initial value to an average value of 40.8 ± 1.28 mmHg (minutes 18 to 21) remaining stable from 22nd minute until the end of the studied period (41.23 ± 0.13 mmHg). The RTR decreases up to minute 16, remaining stable at an 81 % levels from the initial value (73.3 ± 0.04 mmHg/l · min). An increase in the NR is appreciated from the beginning of the simulated haemorrhage, although it is more apparent from minute 15: the values which were reached in a steady state to the

end of the simulation represent a 434 % increase (14.3 ± 0.09 mmHg/l · min). The MTPR follows a parallel behaviour, reaching an increase of 17 % to the end of the observed period (23.2 ± 0.2 mmHg/l · min) (fig. 1).

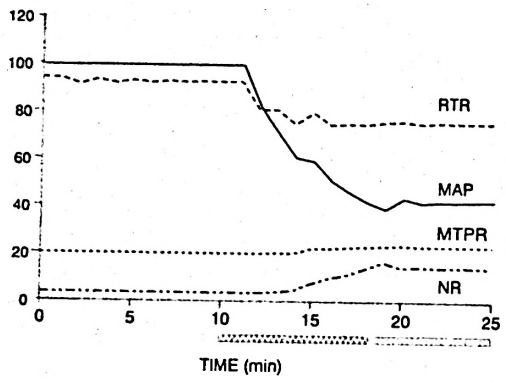

Fig. 1 *Evolution of the mean arterial pressure (MAP), renal total resistance (RTR), resistance derived from the renal nerve activity (NR) and peripheral resistance (MTPR) during the simulation of a haemorrhage.*
MAP is expressed in mmHg and resistances in mmHg/l · min. Bars under x axis denote haemorrhage periods (network weft: 150 ml/min; vertical lines weft: 63 ml/min).

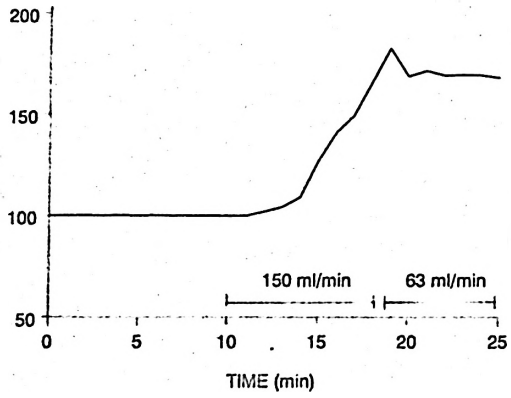

Fig. 2 *Dynamic behaviour of the renal nerve activity (RNA % over basal level) during the simulation of a haemorrhage.*
Lines over x axis denote haemorrhage periods.

The dynamic behaviour of the RNA percentage is represented in figure 2. A maximum increase of 85 % can be appreciated on minute 19, subsequently establishing itself at a 171 % of the basal level.

The values of the RBF which were obtained after subjection of the RTR to the referred conditions are shown in table 1. When the RTR is allowed to vary freely (row RBF[A]), the RBF decreases from 1.077 ± 0.008 l/min (mean ± SD of the values obtained from minutes 1 to 10, pre-

Table I. *Values of mean arterial pressure (MAP) and renal blood flow (RBF) obtained after the simulation of a haemorrhage under different conditions.*
RBF(A): RBF obtained if the renal resistance varied freely; RBF(B): RBF obtained if the intrinsic renal resistance remained constant and NR varied freely and RBF(C): RBF obtained if RTR did not vary.

Time (min)	MAP (mmHg)	RBF (A) (L/min)	RBF (B) (L/min)	RBF (C) (L/min)
1	99.5	1.099	1.099	1.099
2	99.5	1.060	1.076	1.076
3	99.5	1.090	1.076	1.076
4	99.5	1.068	1.076	1.076
5	99.6	1.085	1.076	1.076
6	99.6	1.072	1.076	1.076
7	99.6	1.082	1.076	1.076
8	99.6	1.074	1.076	1.076
9	99.6	1.078	1.076	1.076
10	99.6	1.076	1.077	1.077
11	99.6	1.079	1.077	1.077
12	81.7	0.883	0.883	0.883
13	70.5	0.876	0.764	0.763
14	59.9	0.747	0.651	0.644
15	58.4	0.787	0.636	0.619
16	50.1	0.635	0.547	0.510
17	45.2	0.615	0.495	0.440
18	40.9	0.556	0.450	0.372
19	38.0	0.519	0.419	0.307
20	42.5	0.573	0.468	0.274
21	40.7	0.545	0.448	0.231
22	41.2	0.558	0.453	0.234
23	41.1	0.555	0.452	0.233
24	41.2	0.558	0.454	0.234
25	41.4	0.560	0.456	0.235

haemorrhage period) until 0.557 ± 0.002 l/min, in a steady state at the end of the experiment (mean ± SD, minutes 22 to 25). When the RTR is maintained fixed at its initial level (row RBF[B]), the RBF drops from 1.078 ± 0.007 until 0.454 ± 0.001 l/min (mean ± SD of the prehaemorrhage and final steady state periods, respectively), and, under the fixed intrinsic resistance condition and the NR variable (row RBF[C]), it decreases from 1.078 ± 0.007 to 0.234 ± 0.001 l/min (mean ± SD of the aforementioned periods, respectively).

Discussion

The simulation aimed at emulating an animal experiment reported by KOYAMA *et al.* and making it exportable to human beings. A hypotension situation provoked by a haemorrhage in an animal model (6) is shown in it and a controlled haemorrhage is provoked to obtain an average pressure of approximately 41 % of the initial level, reaching the stated pressure after 8 minutes. The renal nervous activity is recorded simultaneously. Similar decrease percentages in the MAP are obtained by means of the simulated haemorrhage, matching actual conditions. The first 25 minutes of both experiments (real and simulated) are analyzed.

The RNA shows a comparable behaviour to that obtained by KOYAMA (6), except for the maximum increase which is less in the simulated haemorrhage than in the animal experiment. The fact that adapted parameters to the human being were used in the model may explain this difference. The raising of the splanchnic and renal nerve activities during hypotension and haemorrhage situations are known facts, although they are not common for every mammal (4, 7, 15). The increase in the systemic sympathetic activity induces a moderate increase in the peripheral resistance at least in the first stages of shock (14), similar to that obtained by means of simulation.

Sympathetic renal stimulation is also known that induce a vasoconstriction of the kidney vascular tree and, consequently, an increase in its resistance. Nevertheless, there is a trend about the autoregulation of the renal flow by means of the decrease in resistances in these situations. CARLSON and SCHRAMM proved that the speed and the magnitude of vasoconstriction generated by neural stimulus or the administration of vasoactive drugs are clearly reduced (3) during the vasodilation which accompanies the phenomenon of autoregulation. Inspite of the RNA increase, renal resistance can decrease. The total renal resistance in the model shows a decrease (fig. 1), despite the increase in RNA and the NR.

Matching RTR with experimental data is difficult, due to the complexity of the measurement of these variables in experimental conditions in humans. Results obtained by means of simulation under three hypothetical conditions of renal resistance were compared with known physiological values (2, 8), to find out to what extent the decrease of intrinsic renal resistance (vasodilation) counteracts the increase of resistance provoked by simpathetic renal hyperactivity (vasoconstriction) after simulation of the same haemorrhage. It is observed that the behaviour of the RBF, closest to that published in the bibliography, is obtained by allowing the RTR to vary freely, following the suggested equations in the model. Therefore, the initial RBF is reduced to 50 % at pressures close to 40 mmHg. The RBF shows significant inferior values to known ones for practically all the range of the studied pressures, if it is considered that there is no vasodilation or that vasodilation is counteracted by a vasoconstriction of similar magnitude.

In conclusion, an application of a model for the control of the RBF is presented. Its behaviour in hypovolemic shock situa-

tions is comparable to that of animal models. The similitude of the dynamic evolution of certain measurable variables in humans (RBF) with that obtained by simulation leads to induce its usefulness in clinic. Its structure is capable of explaining the paradoxical behaviour of renal resistance against the peripheral resistances in sympathetic hyperactivity circumstances.

Resumen

Se estudia la modificación paradójica de la resistencia renal frente a las resistencias periféricas y al incremento de la actividad simpática en situaciones de shock hipovolémico, usando sendos modelos no lineales del control del flujo sanguíneo renal y de la presión arterial y fluidos corporales, mediante simulación de una hemorragia. Se analiza la variación dinámica de la resistencia renal, de la actividad nerviosa renal y de las resistencias periféricas. Tras comparar los resultados obtenidos con los datos obtenidos con modelos de experimentación animal, puede concluirse: que el modelo que se presenta es útil para su empleo en el análisis de la actividad nerviosa, resistencia y flujo renal en situaciones de shock hipovolémico en humanos y que la estructura de control que se propone puede explicar el comportamiento paradójico de la resistencia vascular renal frente a las resistencias periféricas y al incremento en la actividad nerviosa renal en dichas circunstancias.

Palabras clave: Resistencia vascular renal, Actividad nerviosa renal, Shock hipovolémico, Modelado y simulación.

References

1. Badr, K. F. and Ichikawa, I.: *N. Eng. J. Med.*, 319, 623-629, 1988.
2. Brenner, B. M., Zatz, R. and Ichikawa, I.: In «The Kidney» (Brenner, B. M. and Rector, F. C. eds.). W. B. Saunders Company. Philadelphia, 1987. pp: 93-123.
3. Carlson, D. and Schramm, L. P.: *Am. J. Physiol.*, 235, R64-R75, 1978.
4. Gootman, P. M. and Cohen, M. I.: *Am. J. Physiol.*, 219, 897-903, 1970.
5. Kelleher, S. P., Robinette, J. B., Miller, F. and Conger, J. O.: *Kidney Int.*, 31, 725-730, 1987.
6. Koyama, S., Aibiki, M., Kanai, K., Fujita, T. and Miyakama, K.: *Am. J. Physiol.*, 254, R761-R769, 1988.
7. Morgan, D. A., Thoren, P., Wilczynski, E. A., Victor, R. G. and Mark, A. L.: *Am. J. Physiol.*, 255, H496-H502, 1988.
8. Navar, L. G.: *Am. J. Physiol.*, 234, F357-370, 1978.
9. Roa, L. M., Garrachón, F. y González-Barón, S.: *Rev. esp. Fisiol.*, 45, 221-226, 1989.
10. Roa, L. M., and Garrachón, F.: In «Proc. Twelfth Annual International Conference of the IEEE Engineering in Medicine and Biology Society». (Pedersen, P. and Banu Onaral eds.) Philadelphia, USA, 1990. pp. 1827-1828.
11. Roa, L. M., Gómez-Cía, T. and Cantero, A.: *Burns*, 14, 201-209, 1988.
12. Roa, L. M., Gómez-Cía, T. and Cantero, A.: *Burns*, 16, 25-35, 1990.
13. Roa, L. M.: *Proceedings of the IEEE Computer Society, International Conference on Medical Computer Science/Computational Medicine*, Philadelphia, 1982, pp. 393.
14. Shoemaker, W. C.: In «Pathophysiology of Shock, Anoxia and Ischemia». (Cowley, R. A. and Trump, B. F., eds.). Williams and Wilkins. Baltimore, 1982. pp: 439-446.
15. Skoog, P., Mansson, J. and Thoren, P.: *Acta Physiol. Scand.*, 125, 660-665, 1985.