Editorial Focus Article:
State-space representation of extended Guyton's model
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The work of Moller PW et al. (9), recently published in the American Journal of Physiology-Heart and Circulatory Physiology, has reported that Guyton’s circulatory equilibrium model qualitatively predicts the dynamic response from changing right atrial pressure (RAP) and that RAP acts as back-pressure to venous return. There are some debate as to these ideas (1,2,9). The Editorial Focus Article discussed about these points for further understanding.

Dynamic-state applicability: In cardiovascular system, hemodynamics change acutely, greatly and dynamically in response to physiological perturbations and pathological stress. However, it is difficult to understand how hemodynamic variables are dynamically determined. Regarding to steady-state hemodynamics, Guyton et al. (7) pioneered major advances in understanding cardiovascular system by the circulatory equilibrium model on date back to half a century ago (3-6). They examined the relationship between the steady-state rate of blood flow through the peripheral vasculature and RAP without the complication of changes in total intravascular volume, and characterized the venous return properties of the systemic vein by the venous return curve as a function of RAP (2-6). They also characterized the apparent pumping ability of the cardiothoracic compartment by the cardiac output curve (3-6). In the model, the intersection of the two curves determines equilibrium cardiac output and RAP, indicating a concept of circulatory equilibrium (3-6). However, it has been unclear whether the circulatory equilibrium model is applicable to dynamic-state cardiovascular system. This is an important question in circulatory physiology and clinical cardiovascular medicine.
The recent work of Moller PW et al. (9) have partly answered to the question. They used a closed chest, central cannulation, heart bypass porcine preparation with veno-arterial extracorporeal membrane oxygenation (ECMO) and examined a relationship between RAP and venous return (sum of caval vein flows) by first, changing ECMO pump speed at constant airway pressure; second, clamping of ECMO tubing for the determining mean systemic filling pressure at zero flow; and third, changing RAP by varying airway pressure against a fixed ECMO pump speed, at three volume states of euvoolemia, hypervolemia and hypovolemia (9). They showed a single linear regression between the immediate changes in venous return and RAP within each volume state, regardless of whether RAP was altered by pump speed or airway pressure (9). Cross correlation analysis revealed a highly negative correlation between venous return and RAP (9). As the authors concluded, these results support an idea that venous return property of Guyton's circulatory equilibrium model is applicable to dynamic-state cardiovascular system (9). The idea of dynamic-state applicability of Guyton's venous return property may be consistent with practical clinical data in patients with Fontan circulation reported by Honda et al. (7). The patients had univentricular hearts after total cavopulmonary connection, where systemic and pulmonary vasculatures were directly connected in series in consistent with the heart-lung bypass model. Interestingly, venous return and pressure dynamically and simultaneous changed to opposite direction with each other by respiration and heartbeat (7). This indicates an inverse relationship in dynamic fluctuations of venous pressure and return, probably due to dynamic volume redistribution, observed in human circulatory physiology.

It remains unclear whether cardiac output properties of Guyton's model is valid in dynamic-state condition. For example, acute left ventricular infarction and atrial/ventricular fibrillation acutely reduce left ventricular pump function progressively and thus may flatten cardiac output curve against left atrial pressure (LAP) if Guyton's model is applicable to these dynamic pathological conditions. Further studies are necessary for this point.

Cause and effect: In the recent work (9), Moller PW et al. (9) reported an idea that change in RAP is the cause and change in venous return is the effect in their experiment in that RAP was changed by varying airway pressure, and a conclusion that RAP acts as backpressure to venous return. Contrary to the recent (9) and
previous (1) works by the group of Moller PW, Brengelmann GL has published a
critical analysis of the view that RAP determines venous return (2). He has
reexamined seminal works by Guyton et al. and represented that based on the
open-loop properties of subdivisions of the systems (venous return curve, cardiac
output curve), circulatory equilibrium occurs through the negative feedback
interaction between the subsystems: increasing RAP increases cardiac output in the
cardiac part; increasing cardiac output reduces RAP in the vascular part (2). During
brief periods when venous return and cardiac output are not identical, but total
vascular volume is fixed, the difference is made up by reciprocal exchange of volume
between compliant compartments (2). Thus, superimposing these curves reveals
their intersection at the one level of RAP and flow simultaneously consistent with
independent properties of the heart and vasculature (2). This sounds logical and
reasonable. Accordingly, the idea by Moller PW et al. (9) that change in RAP is the
cause and change in venous return is the effect may fail to interpret their data
adequately. Indeed, the cross correlation analysis in the work by Moller PW et al. (9)
certainly showed negative correlation between venous return and RAP but unclear
in the phase relationship, although the authors described that RAP slightly
preceding changes in venous return. Importantly, RAP and venous return should be
almost simultaneously determined as results of circulatory equilibrium in Guyton's
model: both are the effects.

Extended Guyton's model and state-space representation: The Guyton's model has a
merit to draw a total picture of circulatory system, but is characterized by its
"reductions". The original model lumped various subsystem components including
the right ventricle, pulmonary vascular system and left ventricle, into a single
cardiothoracic compartment, while it lacked the venous return properties of the
pulmonary circulation and the pump ability of the individual ventricles (3-6). Resultantly, redistribution of blood between the systemic and pulmonary
circulations cannot be defined by their original framework (12,13). The original
model thus does not deal with LAP, one of the most important parameters in clinical
managements of heart failure. In addition, defining the circulatory equilibrium is
difficult under complex pathological conditions, including unilateral ventricular
failures (12,13). Accordingly, the original model has been limited to apply to clinical
uses by cardiologists.

Several trials were reported to extend the original circulatory equilibrium model to
actual structure of cardiovascular system. Modified Guyton’s model of
two-compartment model was too complex and has not been used by physicians.
Sunagawa proposed an elegant novel framework of circulatory equilibrium (10,11),
that integrated the venous return properties of systemic and pulmonary
circulations to deal with blood volume redistribution between the two circulations. A
mathematical analysis using a simple linearized model indicated that venous
return forms a flat surface (venous return surface) as a function of RAP and LAP for
a given stressed volume (10,11). The venous return surface parallel shifts upward as
stressed volume is increased and downward as stressed volume is decreased (10,11).
In addition, integrated cardiac output curve was defined as a function of RAP and
LAP (10,11). The intersection of the venous return surface and the integrated
cardiac output curve determines equilibrium cardiac output and RAP and LAP
(10,11), extending the concept of original circulatory equilibrium from
two-dimension (cardiac output, RAP) to three dimension (cardiac output, RAP, LAP).
Here, the essential nature of Sunagawa’s framework is theoretically depicted as
state-space representation (Figure 1) where internal unmeasureable properties of
system (termed as x in Figure 1: total stressed blood volume, pump function,
Systemic arterial resistance) act state vector determine measurable variables
(termed as y in Figure 1: cardiac output, venous return, RAP, LAP, systemic arterial
pressure) as output vector. The total stressed blood volume (termed as V in Figure
1) determines venous return surface uniquely (z intercept is a function of V), while
the pump ability index (a slope of integrated cardiac output curve, termed as SL in
Figure 1) determines a slope of integrated cardiac output curve itself. Here, inputs
to cardiovascular system (termed as u in Figure 1: i.e., drug, physiological stress,
pathological alterations) firstly affect internal unmeasureable properties (x), and
resultantly measurable variables (y) were determined simultaneously as circulatory
equilibrium (Figure 1A-C). There is no cause-and-effect relationship among
measurable variables (y): both RAP and venous return are results of internal
unmeasureable properties (x). The state-space representation has distinguished
merits to develop automated diagnosis system that quantifies internal
unmeasureable properties from measured variables, and further automated
multiple drug infusion system that directly controls internal unmeasureable
properties (x) so that all of measurable variables (y) are simultaneous controlled to
the target levels (Figure 1D). Indeed, the automated system totally normalized
hemodynamics of dogs with acute decompensated heart failure within 30 minutes
(12). The dynamic behavior of controller and plant (dog) (12) indirectly indicate that
state-space representation of extended Guyton's model is applicable to these
dynamic pathological conditions to some extent. However, future studies are
necessary to validate the dynamic-state applicability of extended Guyton's model
(Sunagawa's model) by direct experimental methods.

Another aspect to be addressed is an integration of the Guyton's model and
physiological reflexes; particularly, baroreflexes are most important. For example,
baroreflexes work well to maintain arterial pressure and circulation under
physiological stress (i.e., upright standing (8)) via resetting of central nervous
system processing by dynamically regulating efferent sympathetic/parasympathetic
nerve activities. Accordingly, baroreflexes lead to dynamic changes in pump
function/ability and stressed blood volume. Further studies are needed to
understand these points.

Summary: There are some debate as to dynamic-state applicability and
cause-and-effect relationship between variables in Guyton's circulatory equilibrium
model. The work of Moller PW et al. (9) supports the dynamic-state applicability in
the venous return property of Guyton's model. State-space representation clearly
depicts function structure of cardiovascular system: inputs to the system firstly
affect internal unmeasurable properties of system (total stressed blood volume,
pump function, systemic arterial resistance) and as a result measurable variables
(cardiac output, venous return, RAP, LAP, systemic arterial pressure) were
determined simultaneously as circulatory equilibrium. Accordingly, there is no
cause-and-effect relationship among measurable variables.

References
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3. Guyton AC. Determination of cardiac output by equating venous return curves
   and...


Figure legend

A concept of state-space representation of extended Guyton’s model. A: linear space-state equations in state (top) and output (bottom). $u(t)$ is input to the system. $x(t)$ and $y(t)$ are defined in panel C. $\dot{x}$ is a time derivative of $x$. B: block diagram representation of the linear state-space equations. C: functional structure and contents of internal unmeasureable properties of system ($x$) and measurable variables ($y$). CO, cardiac output; VR, venous return; RAP, right atrial pressure; LAP, left atrial pressure; D: block diagram representation of automated drug infusion system. $rx$ is target values of $x(t)$ calculated from target values of $y(t)$ (not shown). PID controller, proportional-Integral-Differential controller: $u(t)$ is an infusion of multiple drugs (dobutamine, dextran/furosemide, nitroprusside). See references (12, 13) as to further explanations.
State-space representation of extended Guyton's model

\[ \dot{x}(t) = Ax(t) + Bu(t) \]
\[ y(t) = Cx(t) \]

A

\[ u(t) \]
\[ B \]
\[ \dot{x}(t) \]
\[ 1/s \]
\[ x(t) \]
\[ C \]
\[ y(t) \]

B

C

Internal unmeasurable properties
(State vector)

\[ \dot{x}(t) \]
\[ V (total stressed blood volume) \]
\[ S_L (pump ability, slope of CO curve) \]
\[ R (systemic arterial resistance) \]

D

Modified PID controller

State-space representation
(Controlled object)