Electrohydraulic pump-driven closed-loop blood pressure-regulatory system

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Siu KL, Ahn JM, Chon KH. Electrohydraulic pump-driven closed-loop blood pressure regulatory system. Am J Physiol Renal Physiol 296: F1530–F1536, 2009. First published April 9, 2009; doi:10.1152/ajprenal.90756.2008.—In this paper, we describe our design for a new electrohydraulic (EH) pump-driven renal perfusion pressure (RPP)-regulatory system capable of implementing precise and rapid RPP regulation in experimental animals. Without this automated system, RPP is manually controlled via a blood pressure clamp, and the imprecision in this method leads to compromised RPP data. This motivated us to develop an EH pump-driven closed-loop blood pressure regulatory system based on flow-mediated occlusion using the vascular occlusive cuff technique. A closed-loop servocontroller system based on a proportional plus integral (PI) controller was designed using the dynamic feedback RPP signal from animals. In vivo performance was evaluated via flow-mediated RPP occlusion, maintenance, and release responses during baseline and ANG II-infused conditions. A step change of −30 mmHg, referred to as normal RPP, was applied to Sprague-Dawley rats with the proposed system to test the performance of the PI controller. The PI's performance was compared against manual control of blood pressure clamp to regulate RPP. Rapid RPP occlusion (within 3 s) and a release time of −0.3 s were observed for both baseline and ANG II infusion conditions, in which the former condition was significantly better than manual control. We concluded that the proposed EH RPP-regulatory system could fulfill in vivo needs to study various pressure-flow relationships in diverse fields of physiology, in particular, studying the dynamics of the renal autoregulatory mechanisms.

METHODS

Configuring the EH pump. We configured an EH pump to maintain a desired RPP with minimum deviations as well as to deliver a steplike change in RPP in a near instantaneous manner. The system consists of a commercially available EH peristaltic pump (LS brushless computer-programmable drive, Cole-Parmer Instrument, Vernon Hills, IL) with double pump heads, each head having four rollers (LS Easy-Load II pump head 77201-60, Cole-Parmer Instrument). These double pump heads are directly coupled to a drive shaft which can rotate at speeds from 10 to 600 rpm. We used different Y pumps tubing (LS 16, internal diameter = 3.2 mm, Cole-Parmer Instrument) for generating hydraulic pressure, which allows rapid filling and emptying of the silicon occluder. The larger the size of the Y tube, the faster the transfer of fluid to the occluder, but it should be noted that a consequence is greater difficulty in achieving fine adjustments. In this study, we selected the inner diameter of the Y tube for telemetric recordings, which are the ultimate goal as it has been shown that anesthetics depress dynamics of the autoregulatory mechanisms (2).

Many attempts have been made to maintain renal perfusion pressure (RPP) in a desired pressure range, and these include a pneumatic servo-control system (16), a bidirectional DC motor syringe pump system (6), and a unidirectional occlusive mechanical system (15). There are, however, limitations with these approaches as their effectiveness is reduced due to slow dynamic response, inaccurate maintenance of steady-state blood pressure fluctuations, and a bulky hardware system which precludes practical implementation for telemetric usage. A more recent study by Xia et al. (20) used a vascular occluder to servo control RPP in a telemetric setting. However, this system suffers from a slow (∼45–50 s) response time to bring the increased RPP back to preset ranges, thus, making it less useful for evaluating renal autoregulatory dynamics.

To overcome the aforesaid limitations, we present the development of an electrohydraulic (EH) pump-driven closed-loop blood pressure-regulatory system that can be used in vivo. The novelty in the EH pump system stems from the software developed, as it utilizes a commercially available motor and data-acquisition system. The controller software is a user-friendly monitoring program designed to be easily adapted to interested investigators’ laboratories and was programmed using a commercially available software tool known as the LabVIEW 8.0 program (National Instruments, Austin, TX). The software is available free for interested investigators upon request. Our system can be adopted for telemetric use since we use an aortic occluder that is constructed entirely of silicon rubber. The system can occlude and release RPP in ∼3 and 0.3 s, respectively, and maintain desired RPP, based on the designed proportional and integral (PI) feedback controller. These response times indicate that this is a robust controller that results in a rapid step induction of blood pressure signals.

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to be 3.2 mm because this allows the best compromise between delivering fluid in a relatively short time and still being able to make fine adjustments. Figure 1A shows the EH configuration. The pump operation is activated by a monitor program we developed using the LabVIEW 8.0 software tool. The communication between the EH pump and the software is via an RS-232C serial communication port located in the back of the EH pump. Occlusion of RPP is achieved by a mechanical vascular occluder (OC4, In Vivo Metric, Healdsburg, CA) with the following specifications: cuff’s width, thickness, and lumen diameter are 5, 2, and 4 mm, respectively. The double Y tubing described above is directly connected to the vascular occluder. It is our experience that the vascular occluder’s cuff must be inflated at least 50 mmHg more than the systolic pressure for complete occlusion.

The RPP signal was acquired using an analog-to-digital converter (A/D; DT9800 series, Data Translation, Marlboro, MA) controlled by the LabVIEW program. The sampling time of the A/D converter was 5 ms. The LabVIEW program was implemented on a computer running the Windows XP operating system.

**PL controller design.** The PI controller to decrease, maintain, and release the RPP at a predetermined pressure level using the EH pump motor was implemented in LabVIEW 8.0. The PI controller is a closed-loop feedback system which is designed to track the desired reference signal in near real time and with a minimum amount of error at each time step. In general, the proportional controller is designed to provide a fast and large-step compensation to achieve the desired level based on the reference signal. The integral controller is the fine-tuner system designed to eliminate an offset error caused by the over- or undershooting of the desired pressure level caused by the proportional controller. Without the integral controller, the offset error cannot be eliminated. Thus the integral controller is a slow process, and this fine-tuning process can lend itself to slow oscillations as it tries to minimize the tracking of the target error values.

Figure 1B illustrates how the PI controller can be used to control RPP based on the EH pump system. The RPP is the reference signal, and subtraction of the output blood pressure \(U(s)\) signal produces an error signal \([E(s)]\), which is essentially an input to the PI controller. Given the input and output signal, a continuous-time transfer function can be derived below for the PI controller.

\[
\frac{U(s)}{E(s)} = K_p + \frac{K_i}{s} \tag{1}
\]

which can be simplified to

\[
U(s) = K_p\left(1 + \frac{K_i}{K_p} \frac{1}{s}\right)E(s) = K_p\cdot\omega_{pt}\left(\frac{s/\omega_{pt} + 1}{s}\right)E(s) \tag{2}
\]

where \(\omega_{pt} = K_i/K_p\) (expressed in radians/s). In these equations, \(K_p\) and \(K_i\) denote constant gain values associated with the proportional and integrator controller. The 1/s term can be implemented as an integrator. One problem with an integrator is that with time, this value increases to a large value, which can lead to instability. Thus we used an anti-windup algorithm (19) with a saturation value set at 200 (see Fig. 2). Equation 2 above needs to be discretized since we use an A/D converter to control the EH pump. The discretized version of Eq. 2 becomes

\[
U(z) = K_p\left(1 + \omega_{pt}\frac{T_{sample}}{z-1}\right)E(z) = \frac{K_pz + K_p\cdot(\omega_{pt}\cdot T_{sample} - 1)}{z - 1}E(z) \tag{3}
\]

where \(T\) is the sampling time of the PI controller and it is limited by the 4,800-baud rate of the serial communication of the EH motor. Equation 3 can be further modified to a difference equation form

\[
U_{k+1} = K_p\cdot E_{k+1} + K_p\cdot(\omega_{pt}\cdot T_{sample} - 1)\cdot E_k + U_k \tag{4}
\]

The unknown gains, \(K_p\) and \(K_i\) (note \(\omega_{pt} = K_i/K_p\)) were tuned using the Ziegler-Nichols criteria (7) to reduce oscillatory effects and yet generate an appropriately fast reactive pump motor speed. Using a series of animal experiments, the following parameters were derived

\[
K_p = 3, \quad K_i = 30
\]

where \(\omega_{pt} = 0.1 \text{ rad/s} = K_p K_p\), and \(T_{sample} = 10 \text{ ms}\), which was based on the baud rate of the serial communication board of the EH motor.

**Animal preparation for in vivo performance evaluation.** We performed a series of experiments on 10 male Sprague-Dawley rats, weighing 200–300 g, in accordance with the guidelines and practices established for the care and use of research animals at the State University of New York at Stony Brook. The rats were initially

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**Fig. 1.** Schematic diagram of the proportional plus integral (PI) control system. A: optimized electrohydraulic (EH) pump configuration. B: diagram for the servo control system. RPP, renal perfusion pressure.
anesthetized with 3% isoflurane anesthesia, and their body temperature was maintained at 37°C by placing the animals on a temperature-controlled surgery table. We cannulated the trachea, and a stream of 50/50 oxygen/nitrogen mix flowed into their tracheal tube mixed with 1% isoflurane throughout the experiment to maintain the anesthetic state. The right femoral artery was catheterized (PE-50) for the measurement of hindlimb pressure, which is reflective of the RPP. An incision was made on the left flank. The hydraulic vascular occluder was placed around the suprarenal aorta. In some experiments, an ultrasonic flow probe (series 1PR, Transonic Systems, Ithaca, NY) was placed around the left renal artery for the measurement of renal blood flow (RBF). Measurements began 1 h after completion of surgery to allow for the recovery from postsurgical stress.

**Experimental protocol.** In the first set of experiments, the efficacy of the PI controller was compared with manual control \( n = 5 \). RPP was first clamped \( \sim 30 \text{ mmHg} \) below baseline levels for 1 min, after which the clamp was rapidly released. After release, the animal was allowed to recover for 5 min. Typical time traces of the RPP for this clamping protocol are shown in Fig. 3. This clamp and release process was repeated for a total of three trials. After the trials, the occluder was connected to a water-filled syringe for manually controlled hand clamps. This protocol is similar to the PI-controlled clamps, except that the clamping was controlled manually by a syringe. A series of three clamps was also performed.

Figure 2 shows a user interface programmed using the LabVIEW tool. The result is a user friendly application in which the operator inputs a desired reduction in the RPP values and then the software automatically adjusts the pressure using the PI controller. In addition, there are some useful real-time data analysis capabilities including filtering of the data as well as estimation of the power spectrum.

A second set of experiments was performed to assess the system’s ability to function at different RPP set points \( n = 5 \). The protocol is similar to the first set of experiments except that manually controlled clamps were not performed. After a baseline measurement of three PI-controlled clamps, ANG II \( 30 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), Sigma-Aldrich, St. Louis, MO) mixed with 2% albumin and saline solution was infused into the femoral vein to raise baseline RPP. After the RPP and RBF were allowed to stabilize \( \sim 10 \text{ min} \), a second series of three PI-controlled clamps was performed. ANG II infusion was terminated after this second series of clamps, and RPP was allowed to return to baseline levels.

To further test the system’s ability to maintain steady RPP despite pharmacological manipulations to alter RPP, the PI controller was set and engaged at baseline RPP levels, and ANG II was then infused into the animal at the previous flow rate in an attempt to raise RPP. This clamp and release process was repeated for a total of three trials. After the trials, the occluder was connected to a water-filled syringe for manually controlled hand clamps. This protocol is similar to the PI-controlled clamps, except that the clamping was controlled manually by a syringe. A series of three clamps was also performed.

Figure 3 shows representative blood pressure data using the different clamp methods. **Top:** PI-controlled clamp. **Middle and bottom:** 2 investigator-controlled clamps. The middle panel shows a clamp in which the clamp was successful on the initial clamp, and the bottom panel shows a clamp in which there was initial overshoot, followed by a small release of the clamp to bring the blood pressure to desired levels.
response was compared with the ANG II response without engagement of the PI controller.

Data analysis. The collected data were low-pass filtered at 0.5 Hz to remove the cardiac signal from the time traces before analysis. For each clamp, the linear slope and the standard deviation of the RPP fluctuations during the maintenance phase of the PI controller were calculated. Furthermore, the times for the blood pressure to reach desired blood pressure levels as well as the time to reach baseline values were recorded. Trials for each animal for both the PI controller and manual clamping methods were averaged for comparison.

Renal autoregulatory compensation parameters were calculated from RBF for each RPP clamp session. The top and bottom panels of Fig. 4 show typical RBF clamp response time traces under baseline and ANG II infusion conditions, respectively. Note that the RBF traces were plotted as a percentage, where 100% is the mean baseline RBF level. This was done to facilitate comparison between animals and two conditions. This figure has been annotated to detail approaches we have used to calculate various renal autoregulatory compensatory parameters. Four autoregulatory compensatory parameters were calculated from each trace: percent MYO compensation from the clamp release, percent MYO compensation from the clamp engagement, slope of the slower clamp response, and percent compensation of the slower component. The percent MYO compensation from the clamp release was defined as the MYO Release response divided by the complete release compensation, and then multiplied by 100. The percent MYO compensation from the clamp engagement is defined as the MYO clamp response divided by the complete clamp compensation, and then multiplied by 100. The slope of the slower clamp response was defined as the linear slope between the points immediately after the MYO clamp response to immediately before the clamp release. Finally, the percent compensation of the slower component was defined as the slow clamp response divided by the complete clamp compensation, and then multiplied by 100.

The statistical significance for the averaged data was obtained using Student’s t-test or the Mann-Whitney rank sum test when the data did not have equal variance. Difference in variance was tested using the Levenne’s test for equal variance. The paired t-test was used for comparison between baseline and ANG II infusion data from the same animals. In all cases, the statistical significance was set at \( P < 0.05 \).

RESULTS

Table 1 summarizes the RPP and RBF values for the animals. The numbers are reported as means ± SE.

![Fig. 4. Representative renal blood flow (RBF) traces are annotated to illustrate how autoregulatory compensation parameters are calculated. MYO, myogenic mechanism.](image)

Figure 4 shows typical RBF clamp response time traces under baseline and ANG II infusion conditions, respectively. Note that the RPP was clamped to the desired pressure level at the first drop. The bottom panel shows an overclamped trial followed by subsequent adjustments.

Summarized data of RPP from the experiments comparing the performance of the PI controlled clamps vs. the manually controlled clamps are shown in Fig. 5. Data are shown as the means ± SE for five animals. Figure 5 shows the SDs of the signal RPP during the maintenance of RPP phase, which were 1.48 ± 0.176 and 1.54 ± 0.218 mmHg for the PI-controlled and manual clamps, respectively. Figure 5C shows the times needed from the start of clamp to when the RPP attained the desired RPP level, which were 3.26 ± 0.29 and 10.59 ± 3.75 s for the PI-controlled and manual clamps, respectively. Figure 5D shows the times for the RPP to return to baseline levels after the release of the clamp, which were 0.24 ± 0.05 and 0.28 ± 0.04 s for the PI-controlled and manual clamps, respectively. Significant differences in the mean or median and the variance (\( P < 0.05 \)) were found between the slope and the time to desired RPP between the PI-controller and the manual approach.

Although not shown, the same parameters that were measured in Fig. 5 were also measured in the second experiment for the comparison of ANG II-infused animals. Comparison between baseline and ANG II-infused animals showed no statistical significance (\( P > 0.05 \)). This shows that the PI controller performs consistently even with different RPP set points.

Figure 6 shows the typical result for testing the PI controller’s ability to compensate for increases in RPP from pharmacological manipulations. In this figure, ANG II infusion began at 0 min. ANG II infusion resulted in a rise in RPP within 1 min to 170 ± 3.70 mmHg, which then slowly reached a steady state within 10 min to 139 ± 1.02 mmHg. This rise in

Table 1. Average values for RPP and RBF under baseline and ANG II infusion

<table>
<thead>
<tr>
<th></th>
<th>Baseline RPP, mmHg</th>
<th>Maximum ANG II RPP, mmHg</th>
<th>Steady-State ANG II RPP, mmHg</th>
<th>Baseline RBF, ml/min</th>
<th>ANG II RBF, ml/min</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>105 ± 2.87</td>
<td>170 ± 3.70</td>
<td>139 ± 1.02</td>
<td>5.01 ± 0.20</td>
<td>1.49 ± 0.137</td>
</tr>
</tbody>
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Values are means ± SE. RPP, renal perfusion pressure; RBF, renal blood flow.
RPP was not observed in the PI-controlled trace. The results shown demonstrate that the system was able to compensate for relatively large, sudden increases in RPP. The SD of the RPP for 2 min before and after the ANG II infusion was found to be insignificantly different ($P > 0.05$), at 1.51 ± 0.17 and 1.61 ± 0.21 mmHg, respectively.

Summary results from the RBF data calculated according to Fig. 4 between baseline and ANG II clamps are shown on Fig. 7. Statistically significant difference was found in all cases ($P < 0.05$).

**Conclusions**

We demonstrated an effective and yet simple PI servo-controller that can quickly and automatically reduce RPP to desired levels and maintain the pressure despite the opposing compensatory effects. The PI controller was designed to send fluid as quickly as possible to the vascular occluder cuff using an EH pump motor and then fine tune itself to maintain the desired pressure. Using the LabVIEW tool, we designed a user friendly interface in which the operator simply inputs the desired pressure value with the appropriate PI controller gain settings. The program has the ability to filter and estimate the power spectrum of the data in real time. The efficacy of this system was demonstrated by comparing the proposed PI controller to a person who already has had experience in manually controlling the blood pressure using a syringe. Our results indicate that the PI controller provided significantly faster time to a desired RPP level and maintained its value with significantly less variation than human interventions. Furthermore, the system was tested against RPP changes with ANG II infusion, and the results showed that the system performed consistently well even at different set points.

One of the key advantages of the proposed PI-controlled system is the maintenance of the desired RPP, as demonstrated.
in the top panel of Fig. 3 and quantitatively illustrated in Fig. 5A. Compared with human interventions to maintain the desired RPP, shown in the remaining panels of Figs. 3 and 5, the PI controller does a significantly better job. Even with human intervention, there is a monotonic increase in RPP, as shown in the two bottom panels of Fig. 5, and quantitatively illustrated as a rise in slope value compared with no rise in slope with the PI controller in Fig. 5A.

The maintenance of the steady RPP levels during the pressure clamp was achieved by the PI controller using small adjustments on the occluder. With many fine adjustments, there is a concern that they may lead to a greater variance in RPP fluctuation than in normal conditions. However, as shown in Fig. 5B, while the average SD values of the PI-controlled clamps were slightly larger than those of the manually induced clamps, they were not found to be significantly different.

The variance in the time to the desired RPP level was found to be significantly lower in the PI-controlled clamps than with human intervention. This was mainly due to overclamping and subsequent readjustment of the clamps via manual trials, as shown in the bottom panel of Fig. 3. It should be noted that the chance of overshooting the desired RPP decreased with experience. For the PI-controlled clamps, the speed to achieve the desired RPP was consistent across all animals.

ANG II infusion raised the RPP by a maximum of ~65 mmHg and the steady-state value by ~35 mmHg. Figure 6 shows that the proposed PI controller was able to fully compensate for this change with no significant change in the RPP’s variance. Furthermore, RPP clamps performed under the effects of ANG II infusion also yielded no significant difference compared with the baseline. Taken together, this shows that the PI controller system proposed in this work can operate under different physiological conditions.

The representative time traces of RBF clamping experiments shown in Fig. 4 shows that ANG II infusion shifted the distribution of renal autoregulation from a balance of MYO and TGF to a more MYO-dominant behavior. This trend was further seen from the summary data in Fig. 7, where MYO compensation with ANG II infusion was higher than under baseline conditions. With a large increase in RPP, there is a greater need for fast reactivity of MYO than the slower TGF component. This is not surprising, as ANG II has been shown in the past to increase excitability of vessels (10).

A more interesting observation is the slower compensatory mechanism during the step-reduction in RPP (without ANG II infusion). The slow rise in RBF has been noted in several other studies (12), but due to the use of manually controlled clamps, which is not able to curtail the rise in RPP, it was difficult to ascertain whether the rise was due to the RPP itself or the action of the autoregulatory mechanism. With the use of the PI-controlled clamp, RPP was held at a constant level; therefore, we can rule out the possibility of RPP. Thus the slow rise is most likely the action of the TGF.

A previous study by Xia et al. (20) made use of an automatic RPP control system. The response time for that system was ~45–50 s. Furthermore, because the system does not utilize a robust feedback controller, the initial 1–2 min of the controller result in wide variations in RPP. For characterizing renal autoregulatory dynamics where fast control of RRP is required, the controller by Xia et al. (17) would not be applicable. However, this system is useful for studies that involve the control of RPP for long-duration experiments (e.g., telemetric applications).

Although this study was performed in nonsurvival conditions, the occluder used is biocompatible and could be theoretically implanted and used in telemetric survival studies. This PI controller-based occluder has the potential to be especially useful in the application of renal autoregulation studies, where one could take advantage of the fast response time of this system to study the step-response of the autoregulation system under the conscious state.

In conclusion, we have shown that the proposed PI controller offers advantages over the traditional manual clamps. They include consistency in the data and the ability to adjust for small rises in RPP caused by physiological responses to abrupt drops in pressure. Altering the animal condition by the use of ANG II did not significantly alter the performance of the system, suggesting that it can perform under different physiological conditions.

REFERENCES


