Cyclooxygenase inhibition augments central blood pressure and aortic wave reflection in aging humans

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Barnes JN, Casey DP, Hines CN, Nicholson WT, Joyner MJ. Cyclooxygenase inhibition augments central blood pressure and aortic wave reflection in aging humans. Am J Physiol Heart Circ Physiol 302: H2629–H2634, 2012. First published April 13, 2012; doi:10.1152/ajpheart.00032.2012.—The augmentation index and central blood pressure increase with normal aging. Recently, cyclooxygenase (COX) inhibitors, commonly used for the treatment of pain, have been associated with transient increases in the risk of cardiovascular events. We examined the effects of the COX inhibitor indomethacin (Indo) on central arterial hemodynamics and wave reflection characteristics in young and old healthy adults. High-fidelity radial arterial pressure waveforms were measured noninvasively by applanation tonometry before (control) and after Indo treatment in young (25 ± 5 yr, 7 men and 6 women) and old (64 ± 6 yr, 5 men and 6 women) subjects. Aortic systolic (control: 115 ± 3 mmHg vs. Indo: 125 ± 5 mmHg, P < 0.05) and diastolic (control: 74 ± 2 mmHg vs. Indo: 79 ± 3 mmHg, P < 0.05) pressures were elevated after Indo treatment in older subjects, whereas only diastolic pressure was elevated in young subjects (control: 71 ± 2 mmHg vs. Indo: 76 ± 1 mmHg, P < 0.05). Mean arterial pressure increased in both young and old adults after Indo treatment (P < 0.05). The aortic augmentation index and augmented pressure were elevated after Indo treatment in older subjects (control: 30 ± 5% vs. Indo: 36 ± 6% and control 12 ± 1 mmHg vs. Indo: 18 ± 2 mmHg, respectively, P < 0.05), whereas pulse pressure amplification decreased (change: 8 ± 3%, P < 0.05). In addition, older subjects had a 61 ± 11% increase in wasted left ventricular energy after Indo treatment (P < 0.05). In contrast, young subjects showed no significant changes in any of the variables of interest. Taken together, these results demonstrate that COX inhibition with Indo unfavorably increases central wave reflection and augments aortic pressure in old but not young subjects. Our results suggest that aging individuals have a limited ability to compensate for the acute hemodynamic changes caused by systemic COX inhibition.

arterial hemodynamics result in an increased aortic AIx, which is considered an independent predictor of cardiovascular events (20, 24).

AIx and central blood pressure (BP) increase with normal aging; however, the rise in augmentation is more pronounced under certain conditions, such as hypertension and autoimmune diseases (2, 19, 41). Recently, cyclooxygenase (COX) inhibitors, commonly used for the treatment of pain, have been associated with transient increases in the risk of cardiovascular events (13, 23). COX synthesizes a variety of prostaglandins, including PGL2 and thromboxane A2 (TXA2). Vascular cells secrete prostaglandins such as PGL2, a vasodilator, or TXA2, which acts as a vasoconstrictor and thus contributes to peripheral vascular tone in humans (3, 10, 11). Accordingly, the PGL2/TXA2 balance becomes extremely important in the regulation of vascular tone (11). COX inhibitors have been shown to increase total peripheral resistance in healthy adults (45). Because the mediators regulating peripheral vascular tone (i.e., the PGL2/TXA2 balance) may shift with age (32) to favor vasoconstriction (48), adverse cardiovascular effects of COX inhibitors may become more pronounced in an older population. Given the prevalence of COX inhibitor use among the aging population and those with cardiovascular disease, unfavorable cardiovascular changes may have substantial clinical impact. It is currently unknown whether prostaglandins (or COX byproducts) influence aortic wave reflection and mediate the age-related increase in AIx. Accordingly, the aim of this study was to determine the effect of acute COX inhibition on AIx and indexes of aortic wave reflection in young and old healthy adults. Alterations in central arterial pressure after COX inhibition may elucidate the potential role of prostaglandins on central arterial waveform characteristics. We hypothesized that COX inhibition would increase AIx and wave reflection characteristics in both young and old adults.

METHODS

Subjects. Twenty-four volunteers, including 13 young (age: 18–34 yr) and 11 older (age: 59–77 yr) healthy adults, participated in the study. Subjects were nonsmokers, nonobese (body mass index: <30), normotensive, and did not have any underlying cardiovascular, metabolic, or other chronic pathologies (as determined by a health questionnaire and a brief clinical assessment). Blood samples were obtained after a 12-h fast and analyzed for cholesterol and triglyceride concentrations. Prescription medications and over-the-counter medications were reviewed by a physician. Subjects were not taking antihypertensive medication or any other vasoactive medications (except that two older male subjects were on statins). In addition, the use of any nonsteroidal anti-inflammatory drugs, vitamins, and antioxidant supplements were restricted for 10 days before the experimental study day. All subjects were sedentary or recreationally active (no structured training in the previous 3 mo). Older female subjects
were postmenopausal and not on hormone replacement therapy. Young female subjects were studied in the early follicular phase of the menstrual cycle or the low-hormone phase of oral contraceptives. Informed consent was obtained, and subjects were familiarized with the experimental conditions during an initial screening visit. All procedures had ethical approval from the Institutional Review Board of the Mayo Clinic and were performed according to the Declaration of Helsinki.

**Experimental protocol.** The waveform characteristic experiments were conducted in the morning in the Clinical Research Unit at the Mayo Clinic, and subjects arrived to the laboratory after an overnight fast. Subjects were asked to abstain from alcohol, caffeine, or chocolate for at least 24 h before the study. Subjects were in the supine position during instrumentation and measurements. Arterial BP was monitored continuously using finger photoplethysmography (Finometer, TPD Biomedical Instrumentation, The Netherlands) and verified using an oscillographic cuff on the brachial artery. To estimate stroke volume and total peripheral resistance, we used Modelflow analysis from the brachial artery waveform. Briefly, Modelflow computes a beat-by-beat aortic waveform based on nonlinear pressure-volume, pressure-compliance, and pressure-characteristic impedance equations, incorporating age, sex, height, and body mass (46). Cardiac output was calculated as stroke volume \( \times \) heart rate (HR), and total peripheral resistance was calculated as mean arterial pressure/cardiac output. Due to technical difficulties during the Modelflow analysis, the data from one young adult and one older adult were excluded from this analysis. HR from a standard three-lead ECG and \( O_2 \) saturation using pulse oximetry were monitored continuously throughout the study (Cardiocap/5, Datex-Ohmeda, Louisville, CO).

**Central BP and waveform characteristic measurements.** The assessment of arterial wave reflection characteristics was performed noninvasively using the SphygmoCor system (AtCor Medical, Sydney, Australia), as previously described (4, 31). High-fidelity radial artery pressure waveforms were recorded by application tonometry of the radial pulse in the right wrist using a pencil-type micromanometer (Millar Instruments, Houston, TX). Multiple trials of sequential radial pulse waveforms were recorded over a 10-s period for each subject at each time point. Radial BP and arterial waveforms were calibrated from the systolic and diastolic brachial BPs that were taken immediately before by an automated oscillographic device (Cardiocap/5, Datex-Ohmeda). A generalized transfer function to correct for upper limb pressure amplification was used to generate the corresponding aortic pressure waveform and central BP. The generalized transfer function has been validated using both intra-arterially (5, 36) and noninvasively obtained radial pressure waves (14).

Pulse wave analysis of the aortic pressure waveform provided the following key variables of interest: 1) aortic BP; 2) augmented pressure [the amplitude of the reflected wave, which was defined as the difference between the first (forward wave) and second systolic shoulder of the aortic systolic BP]; 3) pulse pressure amplification (the ratio of brachial pulse pressure and central aortic pulse pressure); 4) AIx (the reflected wave amplitude divided by pulse pressure expressed as a percentage); 5) AIx adjusted for a HR of 75 beats/min (AIx at 75 beats/min); 6) round trip travel time of the forward-traveling wave from the beginning of the upstroke of the pressure wave to the inflection point; and 7) left ventricular wasted energy \( (E_w) \), which is the component of the extra myocardial \( O_2 \) requirement due to early systolic wave reflection (Fig. 1) (15, 31). \( E_w \) can be estimated as \( (1.333 \times (\pi/4) \times (\text{augmented pressure} \times \Delta_t)) \), where 1.333 is the conversion factor for mmHg/s to \( \text{dyn} \cdot \text{cm}^{-2} \cdot \text{s}^{-1} \) and \( \Delta_t \) is the time from the inflection point to the dicrotic notch (systolic duration of the reflected wave). Only high-quality recordings, defined as an in-device quality index of >80% (derived from an algorithm including average pulse height variation, diastolic variation, and the maximum rate of rise of the peripheral waveform), were accepted for analysis. In general, two to three measurements were performed to get two measurements with an acceptable quality index. These measurements were conducted before (control) and after COX inhibition (indomethacin (Indo) treatment).

**Drug administration.** Indo, a COX inhibitor, was given orally at a dose of 1.2 mg/kg along with 10 ml simethicone (Maalox) to reduce possible stomach irritation. To allow for adequate absorption time (34), subjects rested for 120 min before repeat measurements were made. At 120 min, the plasma concentrations of Indo are thought to be similar between young and older adults (34).

**Data analysis and statistics.** Subject demographics and baseline characteristics were compared using ANOVA (SigmaStat 12). Primary variables of interest (peripheral and aortic BP and indexes of wave reflection) were compared between groups (young vs. old) and conditions (control vs. Indo) using two-way repeated-measures ANOVA followed by Tukey’s post hoc analysis. In addition, when the change values of pulse wave analysis variables (after Indo treatment) were compared, unpaired \( t \) tests were used to determine significance between young adults and older adults. Significance was set a priori at \( P < 0.05 \).

**RESULTS**

All subjects completed the experimental protocol. Subject characteristics at baseline are shown in Table 1. Young and old
adults were matched for body mass index, lipoprotein concentrations, and BP (Table 2). Although our sample size was small, the calculated powers for the age comparisons were as follows: augmented pressure = 0.99, Alx = 0.99, and left ventricular Ea = 0.97. For control versus Indo comparisons, the calculated powers were as follows: augmented pressure = 0.85, Alx = 0.73, and left ventricular Ea = 0.85.

**Hemodynamic changes with age and Indo treatment.** HR and peripheral and aortic BP were not different between young and old subjects at baseline (Table 2). However, pulse pressure amplification was lower in the older subjects. In the Indo trial, mean arterial pressure increased in both young and older subjects. After Indo treatment, older subjects demonstrated increased aortic systolic BP and increased aortic pulse pressure, whereas these variables were unchanged in young subjects. Older adults also had a significant reduction in pulse pressure amplification (Table 2), which is the ratio of brachial pulse pressure to aortic pulse pressure, whereas there was no change in young adults. This is likely driven by the fact that peripheral pulse pressure only increased 7 ± 6% after Indo treatment, whereas aortic pulse pressure increased 17 ± 7% among older subjects.

Indo treatment increased stroke volume in young adults (99 ± 7 vs. 112 ± 6 mL, P < 0.05), and total peripheral resistance decreased, but this did not reach significance (15.4 ± 1.7 vs. 14.4 ± 1.1 mmHg·l⁻¹·min⁻¹, P = 0.19). Indo treatment did not change stroke volume in older adults (96 ± 14 vs. 95 ± 11 mL, P = 0.45) but tended to increase total peripheral resistance (16.5 ± 2.2 vs. 21.5 ± 4.0 mmHg·l⁻¹·min⁻¹, P = 0.08).

**Aortic wave reflection characteristics.** At baseline, older adults demonstrated higher augmented pressure, aortic Alx, and left ventricular Ea (Fig. 2). Young and older adults had similar values for ejection duration and round trip travel time of the forward-traveling wave from the beginning of the upstroke of the pressure wave to the inflection point (Table 2). After the administration of Indo, there were no changes in wave reflection characteristics in young subjects; however, older subjects demonstrated large increases in augmented pressure, aortic Alx, and left ventricular Ea in addition to a longer ejection duration. After Indo treatment, the absolute changes in augmented pressure, aortic Alx, and left ventricular Ea values (between control and Indo) were significantly higher in older subjects (Fig. 2).

**DISCUSSION**

The major finding of the present study is that aortic augmented pressure and Alx increased after COX inhibitor administration in older subjects but not in young subjects. In addition, older adults demonstrated a substantial increase in central systolic BP and a decrease in pulse pressure amplification after Indo treatment. In contrast, aortic wave reflection characteristics were not changed by COX inhibition in young subjects. Taken together, these results suggest that aging individuals have a limited ability to compensate for the acute central hemodynamic alterations caused by systemic COX inhibition.

COX inhibitors are widely used for the management of pain and are known to have the potential for cardiovascular toxicity. Many of the reported adverse cardiovascular outcomes are associated with COX-2 specific inhibitors, but the underlying mechanisms are unclear (37). Here, we report that a single dose of the nonselective COX inhibitor Indo amplified both central BP and aortic Alx in older adults. These variables are known to be associated with an increased risk of cardiovascular disease (44) and higher mortality in patients with coronary artery disease (6). Therefore, the data presented have high clinical relevance given the prevalence of acute COX inhibitor use among the aging population. Elevated central BP, augmented pressure, aortic wave reflection, and left ventricular Ea were observed in a group of healthy older adults without

<table>
<thead>
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<th>Young Subjects</th>
<th>Older Subjects</th>
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<tbody>
<tr>
<td>Male/female</td>
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<tr>
<td>Age, yr</td>
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<td>Height, cm</td>
<td>176 ± 13</td>
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<tr>
<td>Weight, kg</td>
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<tr>
<td>LDL-cholesterol, mg/dl</td>
<td>95 ± 23</td>
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<tr>
<td>Triglycerides, mg/dl</td>
<td>84 ± 30</td>
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Values are means ± SD; n = 13 young subjects and 11 older subjects. *P < 0.05 vs. young subjects.
history of cardiovascular problems, and this effect may be magnified in patients with known cardiovascular disease.

Elevated AIx with normal aging is well documented (4, 16, 22, 25) and largely attributed to structural and functional changes within the central elastic arteries (25, 30). Elevated AIx with advancing age may be due to the age-related increase in central arterial stiffness, which influences the timing of the reflected wave. Potential mechanisms for the age-related increase in central arterial stiffness include the following: the deterioration of elastin components of the arterial wall (17), hypertrophy of vascular smooth muscle cells (17), and reduced endothelium-dependent vasodilation (33). Stiffening of the central arteries results in faster propagation of wave travel to the peripheral arteries and an earlier return of the reflected wave. We found increases in aortic AIx and reduced pulse pressure amplification in a group of healthy older adults without confounding cardiovascular disease risk factors. It is important to note that differences between young and older subjects during the control condition were only observed for aortic AIx, pulse pressure amplification, augmented pressure, and left ventricular E\textsubscript{w}. After Indo treatment, these age-related differences remained, and additional differences between young and old adults emerged for central BPs.

In this study, we used an acute administration of oral Indo to block both vasodilating and vasoconstricting prostaglandins. Indo is typically used for the management of pain and has been shown to increase BP with several weeks of use in borderline hypertensives (38) and increase total peripheral resistance in healthy adults (45). Similarly, Indo increased mean arterial pressure measured at the brachial artery in both young and older subjects in the present study. In addition, older adults demonstrated higher aortic systolic BP and pulse pressure during Indo treatment compared with young adults. Therefore, one underlying mechanism of the increase in central BP is due to an increase in total peripheral resistance. In support of this, plasma levels of PGE\textsubscript{2} have been inversely correlated with total vascular resistance (38) and a reduction in PGE\textsubscript{2} concentration has been associated with an increase in vascular resistance (29) in previous studies. In our study, there was a tendency for the older adults to increase total peripheral resistance (P < 0.08), whereas young adults did not exhibit a change. Higher vascular resistance results in earlier wave reflection from the periphery (47) and may also explain the increase in augmented pressure, AIx, and left ventricular E\textsubscript{w} in older adults in the present study. Young adults demonstrated no significant changes in total peripheral resistance, augmented pressure, AIx, or left ventricular E\textsubscript{w} by COX inhibition, indicating that central wave reflection characteristics were unaffected. That is, COX inhibition in older adults appears to further amplify the age-related increase in wave reflection, whereas there is little to no change in young adults.

Because the regulation of peripheral vascular tone is mediated by multiple factors, blocking prostaglandin synthesis will require a greater reliance on other compensatory mechanisms to maintain the regulation of vascular tone. Therefore, potential mechanisms for the age-related difference in central hemodynamics after COX inhibition include reduced nitric oxide (NO) bioavailability (42) and lower tetrahydrobiopterin (BH\textsubscript{4}) con-

Fig. 2. Left: absolute values for AP, aortic AI, and left ventricular E\textsubscript{w}. Right: magnitude of changes between control and indomethacin trials for young and older subjects. *P < 0.05 vs. young subjects; †P < 0.05 vs. control.
The present study, where Indo treatment increased left ventricular aging (9) and promotes the conversion of NO to peroxynitrite synthase (40) and ensures the synthesis of NO instead of concentrations (8), both of which result in impaired vasodilatory function. BH₄ is an essential cofactor for endothelial NO synthase (40) and ensures the synthesis of NO instead of endothelial NO synthase, producing free radicals. Oxidative stress within vascular endothelial cells also increases with aging (9) and promotes the conversion of NO to peroxynitrite, which may inactivate BH₄, thereby diminishing NO bioavailability (18) and potentially increasing central arterial stiffness. Given these potential age-related changes, fewer vasodilatory mechanisms would be available to offset the vasoconstrictor response to COX inhibition, resulting in a greater augmentation of the reflected wave and therefore central BP. Thus, the vasoconstricting effect of Indo on the peripheral vasculature likely produces the increase in peripheral wave reflection in older adults (38, 45). Additionally, Indo has been shown to induce coronary vasoconstriction and decrease myocardial blood flow in adults with coronary artery disease (12, 35). It also increases myocardial O₂ consumption (35), analogous to the present study, where Indo treatment increased left ventricular $E_{\text{a}}$ only in older adults. Although the previous studies evaluated the effects of COX inhibition in patients with coronary heart disease, the negative effects of Indo may also be amplified by the alterations in central and peripheral hemodynamic characteristics.

Our results suggest that older healthy adults have a limited ability to compensate for the acute hemodynamic changes induced by COX inhibition using Indo. It is possible that baroreflex sensitivity is impaired in older adults, and the baroreflex is not sensing or responding to the acute increase in central BP. Baroreflex sensitivity decreases with advancing age and is associated with central arterial stiffness (7, 26, 27). Mechanistically, baroreflex sensitivity likely depends on the deformation or distension of the artery in response to acute pressure changes. In this context, an acute increase in stiffening will reduce distensibility within the carotid sinus or aortic arch, thereby diminishing the stimulus evoking the baroreflex response. In healthy young adults, COX inhibition (with ketorolac) does not change baroreflex sensitivity (28); however, animal studies have suggested that prostacyclin enhances baroreflex sensitivity slopes and that Indo blunts the baroreflex response to increasing carotid sinus pressure (21). To our knowledge, the effects of COX inhibition on baroreflex sensitivity in older adults have not been studied.

There are several limitations in the present study. First, we evaluated the effects of oral Indo, which was administered according to body weight, but is possible that these results may be affected by differences in absorption time among individuals. Plasma levels of Indo were not taken, and it is possible that absorption times resulted in different plasma levels. However, we used a typical drug wash-in period, similar to a previous study (49). In addition, we did not use a placebo-controlled double-blinded study design; instead, each subject was used as his or her own control, and young adults (where only slight changes were noted) served as a control group for older adults. We administered only one typical dose of Indo; therefore, our results may not extend to long-term use of this drug. In addition, we did not evaluate the effects of other COX inhibitors to determine if this effect is isolated to nonselective Indo. A comparable dose of a COX-2-specific inhibitor may elicit a larger reduction in vasodilating prostaglandins and a greater effect on peripheral wave reflection characteristics. Nevertheless, the importance of the age-specific differences in the augmented central BP response to COX inhibition indicates 1) the usefulness of central BP as a tool for measuring the “true impact” of an intervention, particularly in aging or at risk adults; and 2) other commonly used nonsteroidal anti-inflammatory drugs that may affect hemodynamics and could have greater detrimental effects in older adults or individuals with cardiovascular problems.

In conclusion, these results demonstrate that COX inhibition with Indo unfavorably increases central and peripheral wave reflection and augments aortic pressure in old subjects but not in young subjects. Our results suggest that aging individuals have a limited ability to compensate for the acute hemodynamic changes caused by systemic COX inhibition.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS


REFERENCES


