Comparison of Hypoxia and Ouabain Effects on the Myocardial Uptake Kinetics of Technetium-99m Hexakis 2-Methoxyisobutyl Isonitrile and Thallium-201

Denis J. Meerdink and Jeffrey A. Leppo

Department of Nuclear Medicine and Department of Medicine, Cardiology, University of Massachusetts Medical Center, Worcester, Massachusetts

Effects of hypoxia and ouabain on transcapillary exchange of [^{99m}Tc]hexakis (2-methoxyisobutylisonitrile) [SESTAMIBI, also known as MIBI or HEXAMIBI] and ^{201}Tl were investigated with indicator-dilution studies using isolated rabbit hearts. Peak myocardial extraction (Emax), permeability-surface area products (PScap), and net myocardial extraction (Enet) were compared among serial injections during constant coronary flows. Overall, measures of transcapillary transport (Emax and PScap) for SESTAMIBI were significantly lower ($p < 0.001$) than those simultaneously determined for thallium, but estimates of tissue retention (Enet) for SESTAMIBI and thallium were not statistically distinguishable. Hypoxia had no significant effect on mean (±s.d.) Emax for SESTAMIBI (0.31 ± 0.13) or thallium (0.59 ± 0.11), nor on mean PScap or Enet values. Ouabain (1.5×10^{-7} *M* and 1.5×10^{-6} *M*) had no effect on SESTAMIBI or thallium Emax (respectively, 0.29 ± 0.08 and 0.60 ± 0.05) or on PScap for SESTAMIBI. Thallium PScap was depressed with higher ouabain dose (control, 1.22 ± 0.40; high ouabain, 1.06 ± 0.41 ml/min/g; $p < 0.01$). Ouabain also caused a significant and progressive increase in average SESTAMIBI Enet (control, 0.23 ± 0.10 to high ouabain, 0.33 ± 0.12; $p < 0.05$), but depressed thallium Enet (control, 0.38 ± 0.14 to high ouabain, 0.32 ± 0.18; $p < 0.01$). These results suggest myocardial metabolic and/or functional status have minor influence on transcapillary transport of SESTAMIBI and thallium, but significantly affects cellular retention.

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Technetium-99m- (^{99m}Tc) labeled agents have been proposed as alternatives to thallium-201 (^{201}Tl) for imaging myocardial perfusion imaging because of better photon statistics, Anger camera imaging properties, cost, and clinical availability (*1–4*). Clinical images from [^{99m}Tc]-labeled isonitriles compare favorably to those obtained with thallium (*3,5*). Specifically, [^{99m}Tc] hexakis (t-butylisonitrile) (TBI) and its ether derivate, [^{99m}Tc]hexakis 2-methoxyisobutyl isonitrile (SESTAMIBI, also known as MIBI, HEXAMIBI, or RP-30; DuPont Company, No. Billerica, MA), have suitable kinetic characteristics and have shown good potential in preliminary clinical studies. SESTAMIBI, in particular, may have appeal for cardiac studies because of its low lung extraction compared to TBI (*6*).

The interpretation of perfusion images of cardiac uptake for these agents is facilitated from knowledge of the capillary exchange process. To assume that clinical perfusion images realistically represent myocardial blood flow, it must be known that the imaging agent is deposited in myocardial tissue in proportion to the blood it receives, and that this deposition is unaltered by metabolic or functional abnormalities. No previous studies have determined the effects of metabolic aberrations on the transcapillary transport of both thallium and SESTAMIBI in the same hearts with constant coronary flow. Accordingly, the goal of this report was to determine the flow-independent effects of hypoxia and ouabain on myocardial uptake kinetics of these two perfusion agents.

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For reprints contact: D. J. Meerdink, PhD, Dept. of Nuclear Medicine, University of Massachusetts Medical Center, 55 Lake Ave., North, Worcester, MA 01655.

MATERIALS AND METHODS

Experimental Preparation

Surgery and perfusion. An isolated, isovolumetrically-contracting rabbit heart preparation, utilizing methods previously described in detail (*7–9*), was used for all experiments. Briefly, male New Zealand white rabbits (1.5–2.5 kg) were heparinized (600 IU/kg i.v.) and anesthetized (sodium pentobarbital, 40 mg/kg i.v.), and the hearts were quickly removed and mounted on a perfusion apparatus (*9*). For hypoxia experiments, the nonrecirculating perfusate consisted of a modified Krebs-Henseleit bicarbonate buffer, pH 7.4, that contained (m*M*): NaCl, 122; $NaHCO_3$, 22; glucose, 5.5; KCl, 4.7; $MgSO_4$, 1.2; $CaCl_2$, 2; KH_2PO_4, 1.2; lactate (neutralized with NaOH), 1; and Na_2EDTA, 0.4. Normoxic buffer and hypoxic buffer were bubbled with 95% O_2/5% CO_2 and 95% N_2/5% CO_2, respectively, for a minimum of 30 min prior to heart perfusion. For ouabain experiments, the perfusate was blood obtained from a second heparinized, anesthetized rabbit as previously described (*8,9*), which recirculated except when indicator dilution injections were made. The blood passed through a membrane oxygenator that was gassed with a 3% CO_2 and air mixture. During experimentation, blood gas measurements were made every 30–40 min, and appropriate adjustments were made with supplemental O_2 and bicarbonate to maintain blood pH. P_{O2}, and P_{CO2} in the physiologic range. Glucose levels were also monitored and adjusted as needed to maintain approximately 100 mg/dl.

For both hypoxia and ouabain protocols, mean coronary perfusion pressure was maintained at 100–125 mmHg by a constant flow pump. A thermistor and pacing catheter were placed in the right ventricle via the right atrium to monitor tissue temperature (37 ± 1°C) and maintain a heart rate of at least 180 bpm. A plastic cannula was also placed in the right ventricle via the pulmonary artery for collecting coronary sinus drainage samples and measuring coronary flow. A latex rubber balloon was inserted and secured into the left ventricle, and filled with saline until an end-diastolic pressure of 5–10 mmHg was recorded. A plastic cannula, placed in the left ventricle at its apex, drained aortic valve leakage, and Thebesian vein flow. Mean aortic pressure, left ventricle (LV) pressure, and the first derivative of LV pressure were continuously recorded. The experimental protocols (described below) began after temperature, ventricular pressure, contraction rate, coronary flow, and aortic pressure stabilized.

SESTAMIBI preparation. The SESTAMIBI salt [supplied by DuPont Company; (*2*)] and formamidine sulfinic acid (FSA) were prepared as a 4 mg/ml and 0.4 mg/ml solution, respectively, in distilled water. A 0.5-ml aliquot of each of the SESTAMIBI and FSA solutions were combined in a nitrogen-purged vial, and ~0.2–0.4 ml of $^{99m}TcO_4^-$ (370 MBq, 10 mCi) was added. The vial was quickly placed in boiling water for 10–15 min and then allowed to cool to room temperature. Binding efficiency was evaluated by thin layer chromatography (*9*), and was always ≥95%.

Isotope injection and sample collection. The indicator cocktail, consisting of a mixture of 20 μCi (0.74 MBq) of indium-111- (^{111}In) labeled albumin (*10*), 35 μCi (1.3 MBq) of $^{201}TlCl$, and 90 μCi (3.3 MBq) of [^{99m}Tc]SESTAMIBI dissolved in perfusate, was thoroughly mixed and a 0.3-ml bolus was loaded into an injection loop that ran parallel to and joined with the aortic inflow with three-way valves. Isotope injection proceeded by rapidly turning the three-way valves so that the bolus was as homogeneously distributed as possible to both coronary arteries. Coronary venous effluent was collected into preweighed plastic tubes at 1.2- to 5-sec intervals (depending on flow rate) over a 0.5–4 min collection time. Coronary flow was measured before and after injections; results were discarded if flows changed more than 10%. Full sample weights were measured, and isotope activities were determined in each sample along with a 0.1-ml aliquot of each injectate by a gamma well counter with corrections for energy crossover, time, background, and physical decay during the counting process. When multiple injections (at constant flow) were made in an individual heart, isotope backgrounds were <1% of peak activity in all instances. In addition, the wet weight of a portion of the left ventricular free wall was determined for subsequent estimation of the tissue water fraction (*7*).

Myocardial transport analysis. For each injection, transcapillary exchange estimates were determined using standard indicator dilution techniques and equations (*9,11,12*). Briefly, normalized transport function curves for albumin [reference, $h_R(t)$] and for SESTAMIBI and thallium [diffusible tracers, $h_D(t)$] were calculated from the general equation, $h(t) = F_s \cdot C(t)/q_o$, where Fs is plasma flow (ml/min/g), t is time (sec), C(t) is isotope activity, and q_o is injected dose. The instantaneous fractional extraction [E(t)] for SESTAMIBI and thallium was calculated for each sample with the equation, $E(t) = 1 - h_D(t)/h_R(t)$, and the capillary permeability-surface area product (PScap, ml/min/g) was calculated with the equation, $PScap = -F_s \cdot \log_e(1-E_{max})$ (*13*). Emax was defined as the maximum E(t) of diffusible tracer observed up to the peak $h_R(t)$, which is the best estimate of average functional extraction (*11,14*). Net tissue extraction (Enet), an estimate of tissue retention, was calculated from normalized time integrals of transport function differences between reference and diffusible tracers with the equation (*14*): $Enet = \int_0^t[h_R(t)-h_D(t)]d\tau / \int_0^t h_R(t)d\tau$, where t was defined as the time (sec) when 99.99% of the albumin reference had emerged in the venous effluent, and τ was the dummy variable for integration.

Results were analyzed with paired t-tests and repeated-measures analysis of variance routines (*15*) and comparisons made among treatments within the hypoxia or ouabain experimental series (*16*).

Experimental Protocols

Hypoxia. To study the effects of hypoxia, eight hearts were initially perfused with buffer gassed with 95% oxygen/5% carbon dioxide and allowed to stabilize for ~10 min, after which the control injection of tracer cocktail was made. The perfusion buffer was then changed to one made hypoxic by gassing with 95% nitrogen/5% carbon dioxide; after 2 and 5 min of hypoxic perfusion, the first and second experimental injections were made while coronary flow remained constant.

Ouabain. Ouabain effects were evaluated in 11 hearts perfused with recirculating blood at constant flow. Following a stabilization period of ~15 min, a control injection was made, after which a ouabain solution was infused into the system over 5 min so that a concentration of 1.5×10^{-7} *M* (LOW dose) was achieved in the recirculating blood. This typically resulted in a transient rise in +dP/dt, but as LV end diastolic pressure began to increase, positive inotropic response could

not be sustained. After the first ouabain dose circulated at least 15 min, the first experimental injection of indicator cocktail was made. A second dose of ouabain was given over 5 min, increasing the ouabain concentration to 1.5×10^{-6} *M* (HIGH dose). The second experimental dilution study was made after the HIGH dose circulated at least 15 min. These ouabain concentrations were based on therapeutic (LOW) and toxic (HIGH) concentrations (*17,18*). Ventricular ectopy increased greatly during these infusions, strongly implying that the ouabain infusions produced pharmacologic concentrations.

Results were reported as mean (±s.d.), and considered significantly different with a probability of 0.05 or less. Statistical analysis included the paired Student's t-test and analysis of variance (uni- and multi-variant, and repeated measures) (*16*), and was performed using the Statistical Analysis System (*15*).

RESULTS

Average (±s.d.) results for the hypoxia and ouabain studies (respectively) include: body weight, 2.22 (±0.18) and 1.67 (±0.11) kg; wet heart weights, 6.03 (±0.55) and 5.41 (±0.36) g; and tissue water fraction, 0.85 (± 0.01) and 0.73 (±0.01). Significant differences ($p < 0.02$) existed between hypoxia and ouabain experiments for only body weight and tissue water fraction.

Hemodynamics

Average (±s.d.) results for hemodynamic measurements appear in Table 1. These parameters were not affected by the injection of isotope cocktail during hypoxia or ouabain experiments (data not shown). Repeated-measures analysis of variance of control, 2-, and 5-min hypoxia injections indicate no significant change in coronary perfusion rates, but significant decreases ($p < 0.001$) existed in aortic pressure, peak systolic pressure, +dP/dt, and −dP/dt. The 30% decline in aortic pressure (i.e., perfusion pressure) after 2 min of hypoxic perfusion was not further depressed at 5 min of hypoxia, which indicates a prompt and maximal reduction in vascular resistance. The progressive decline in developed systolic pressure, +dP/dt, and −dP/dt as well as an increase of end diastolic pressure after 2 and 5 min of hypoxia, reflects the severe functional compromise induced by hypoxia. In ouabain experiments, no significant change was noted in perfusion rate, but a small increase in end diastolic pressure reached statistical significance ($p < 0.05$).

Indicator Dilution Analysis

Examples of the indicator transport functions [h(t)] and instantaneous extraction [E(t)] appear in Figure 1 for a control injection. Differences in the height and shape of the h(t) and E(t) curves between thallium and SESTAMIBI suggest fundamental differences in their mechanisms of transcapillary transport. The h(t) curve for thallium is much lower than the SESTAMIBI h(t), which indicates a higher peak extraction (Emax) for thallium.

The tail portion of the h(t) curves also reveal fundamental differences in the extravascular distribution of thallium and SESTAMIBI. The transport function curve [h(t)] for thallium crosses and remains above the reference albumin, which indicates a net flux of initially extracted thallium from the myocardial tissue back into the vascular space. In contrast, SESTAMIBI h(t) remains below the albumin reference h(t) throughout the observation period, indicating relatively little back diffusion of SESTAMIBI.

The E(t) curves for thallium and SESTAMIBI are also quite different, which also reveals their different

TABLE 1
Hemodynamic Results*

	Coronary Flow (ml/min/g)	Aortic Pressure (mm Hg)	Peak Systolic Pressure (mm Hg)	End Diastolic Pressure (mm Hg)	+dP/dt (mm Hg/s)	−dP/dt (mm Hg/s)
Hypoxia						
Control	5.52 (1.47)	47.0 (10.3)	77.9 (12.6)	6.5 (0.9)	1630 (284)	1362 (327)
2 min.	5.49 (1.51)	39.6 (15.4)	50.8 (28.4)	9.3 (6.4)	1176 (564)	877 (493)
5 min.	5.48 (1.56)	32.3 (11.6)	32.9 (12.9)	12.3 (10.1)	586 (234)	418 (146)
p**	NS	<0.001	<0.001	<0.001	<0.001	<0.001
Ouabain						
Control	1.96 (0.63)	120.4 (25.3)	63.3 (18.0)	12.1 (5.4)	1261 (546)	658 (424)
LOW Dose	1.96 (0.62)	131.1 (27.8)	62.8 (21.9)	18.4 (10.6)	1196 (812)	658 (563)
HIGH Dose	1.89 (0.69)	154.0 (37.8)	68.0 (29.4)	19.9 (15.0)	1602 (1292)	800 (676)
p**	NS	<0.01	<0.03	NS	NS	NS

* Mean ± s.d.
** Probability of equality as determined by repeated-measures analysis of variance (15).
NS = not significant.

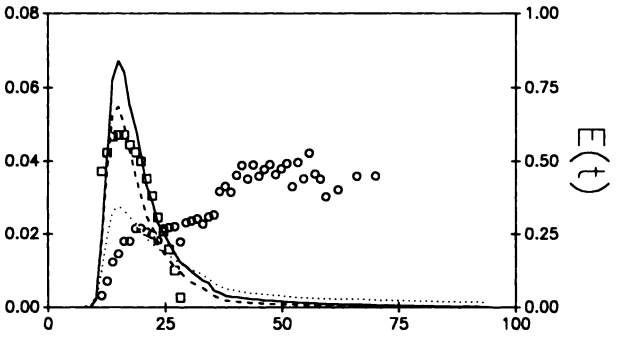

FIGURE 1
Representative plot of the transport function [h(t)] and instantaneous fractional extraction [E(t)] versus sampling time. The left ordinate are the h(t) values for [^{111}In]albumin (solid line), [^{99m}Tc]SESTAMIBI (dashed line), and ^{201}Tl (dotted line). The right ordinate are the E(t) values for [^{99m}Tc]SESTAMIBI (open circles) and ^{201}Tl (open squares).

transport mechanisms. Thallium E(t) has an early maximal plateau phase followed by rapid fall, which is typical for cations, while SESTAMIBI E(t) displays an early rise and sustained, slowly rising plateau throughout the h(t) curve.

Extraction. Average (±s.d.) maximal instantaneous extractions (Emax) of thallium and SESTAMIBI appear in Figure 2. For all injections in both hypoxia and ouabain experiments, SESTAMIBI Emax determinations were significantly lower ($p < 0.001$) than concurrently-measured thallium values, averaging 48% and 43% lower ($p < 0.001$) in hypoxia and ouabain experiments, respectively. In hypoxia experiments, analysis of variance (repeated measures) and paired t-tests revealed no significant Emax differences for thallium or SESTAMIBI in either experimental injection from their respective control determinations (Fig. 2A). In ouabain experiments (Fig. 2B), Emax for SESTAMIBI tended to increase and thallium tended to decrease, although no statistically significant differences were revealed between experimental injections and their respective controls.

Permeability. Figure 3 illustrates the mean (±s.d.) PScap determinations for thallium and SESTAMIBI for hypoxia and ouabain experiments. PScap for SESTAMIBI averaged 58% of those for thallium for hypoxia experiments and 48% lower in ouabain experiments. In hypoxia experiments (Fig. 3A), PScap values for SESTAMIBI were significantly less ($p < 0.001$) than simultaneously-determined thallium estimates in each of the three injections. Hypoxia treatment also did not significantly change SESTAMIBI or thallium values from their respective controls. In contrast, PScap averages for SESTAMIBI in ouabain experiments (Fig. 3B) were significantly less ($p < 0.02$) than thallium only for control and LOW dose injections, but not for HIGH dose injections. In addition, thallium PScap declined

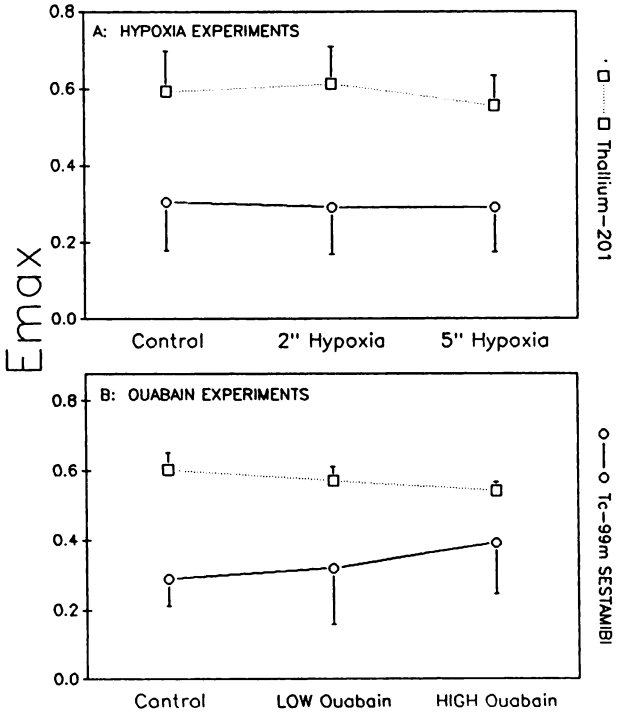

FIGURE 2
Average (±s.d.) Emax estimates for [^{99m}Tc]SESTAMIBI (open circles) and ^{201}Tl (open squares) for hypoxia (panel A) and ouabain (panel B) experiments. See text for treatment descriptions.

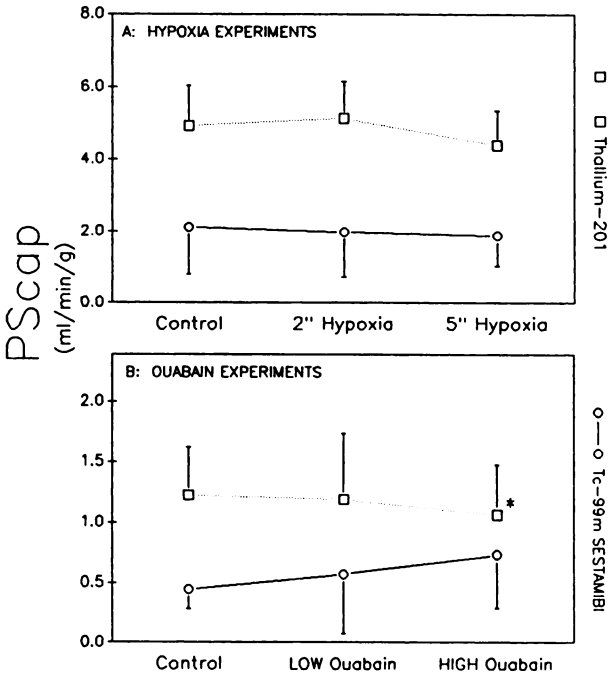

FIGURE 3
Average (±s.d.) PScap estimates for [^{99m}Tc]SESTAMIBI (open circles) and ^{201}Tl (open squares) for hypoxia (panel A) and ouabain (panel B) experiments. See text for treatment descriptions. (* indicates paired difference ($p < 0.015$) from control.)

significantly ($p < 0.02$) from control during the HIGH ouabain dose. PScap values for SESTAMIBI tended to increase with ouabain dose level, but this rise did not achieve significance.

Retention. Average (±s.d.) Enet values for hypoxia and ouabain experiments appear in Figure 4. Unlike Emax and PScap computations, SESTAMIBI Enet estimates were greater than or approximately equal to those for thallium. Paired analysis revealed no significant differences in Enet estimates between SESTAMIBI and thallium for any hypoxia or ouabain injection, except for the ouabain control (SESTAMIBI < thallium; $p < 0.01$). Although the average Enet for SESTAMIBI tended to increase with hypoxia (Fig. 4A), a difference from control reached statistical significance only for 2-min hypoxia determinations ($p < 0.05$) because of the relatively large variation in 5-min hypoxia estimates. SESTAMIBI Enet in ouabain experiments (Fig. 4B) also increased and reached statistical significance with HIGH ouabain dose (<0.01). In contrast, a significant and progressive decline in thallium Enet was noted for both LOW and HIGH ouabain doses ($p < 0.01$).

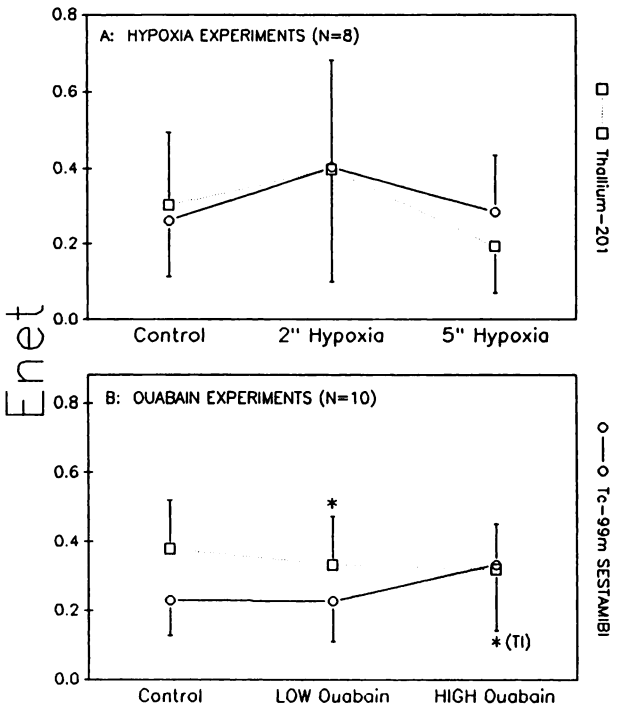

FIGURE 4
Average (±s.d.) Enet estimates for [^{99m}Tc]SESTAMIBI (open circles) and ^{201}Tl (open squares) for hypoxia (panel A) and ouabain (panel B) experiments. See text for treatment descriptions. (* indicates paired difference ($p < 0.015$) from control.)

DISCUSSION

The present study demonstrates that hypoxia and ouabain have small but significant effects on the myocardial transcapillary transport of SESTAMIBI and thallium in the perfused rabbit heart model. However, net cellular retention of these two tracers is more sensitive to hypoxia and ATPase inhibition than peak extraction or permeability.

Isolated Heart Model: Critiques

Using hemoglobin-free buffer in hypoxia experiments necessitates a two- to three-fold increase in the normal (2-4 ml/min/g) coronary perfusion rate of a normal rabbit heart (*19*) so that the tissue receives adequate oxygen supplies. Using protein-free buffer in hypoxia experiments also caused an average 16% higher tissue water fraction than what was observed using blood perfusate (ouabain studies). Both increased perfusion rate and tissue edema would affect kinetic estimates (*9*). Specifically, during high flows and increased interstitial space, peak extraction (Emax) and permeability (PScap) could be underestimated. These alterations in buffer-perfused hearts makes the comparison of absolute transport rates with studies using blood perfusates difficult and therefore was not attempted nor implied.

Measures of Treatment Effect

Hypoxia. Previous reports of hearts perfused with hypoxic buffer (*20*) have shown flow-independent hemodynamic alterations similar to those observed in the present study (Table 1), which demonstrate the severe cellular functional compromise induced by hypoxic perfusion. Although function deteriorated rapidly with hypoxic treatment, flow rate remained constant. Therefore, observed changes in transcapillary transport in this study cannot be explained by fluctuations in flow.

Ouabain. Ouabain produced a significant change in aortic pressure and peak systolic pressure (Table 1), but no significant increase in +dP/dt was observed. As previously noted, an increase in positive or negative dP/dt was not sustained, which might indicate insufficient drug levels. However, the ouabain doses are in the therapeutic and toxic ranges (*17,18*). In other unpublished studies, further increases in ouabain dose produced ventricular fibrillation and rapid heart failure. Although the drug concentration in the perfusate was not measured directly, the doses appear to have achieved a pharmacologic effect. With these considerations, we assumed the hearts received adequate ouabain to achieve functional inhibition of Na^+/K^+ ATPase.

Indicator Dilution Analysis

Transcapillary exchange. These experiments confirm previous results (*9,20*) by demonstrating that SESTAMIBI transcapillary exchange is significantly less than that of thallium. In the present studies, peak extractions (Emax) and capillary permeability-surface

area products (PScap) for SESTAMIBI averaged ~40% and 30%, respectively, of thallium. These relationships in Emax and PScap were unaffected by either hypoxia or ouabain. However, in ouabain experiments, opposing effects are noted for SESTAMIBI Emax (increase) and thallium (decrease). This trend becomes statistically apparent in the Enet analysis (below).

The control Emax estimates for thallium of about 0.60 (Fig. 2) compare to maximum extractions of above 0.70 in previous reports (*7*). The lower thallium extraction observed in the present studies is probably a result of higher myocardial flow since rabbit hearts have intrinsic perfusion rates of two to three times that of other species (*19*), which appreciably reduces peak thallium extraction.

In a previous study with cultured heart cells (*21*), ouabain or other metabolic inhibitors had little effect on SESTAMIBI or thallium uptake. Thallium extraction has been reported to be insensitive to hypoxia in perfused rabbit hearts (*20*) and open-chest dogs (*22*). Weich et al. (*23*) observed a drop of 11% in thallium extraction fraction during hypoxia in open-chest dogs, but coronary flow was not constant and could increase enough during hypoxia to account for the calculated decrease in extraction. Therefore, it seems reasonable to conclude that peak SESTAMIBI and thallium extraction fraction is relatively insensitive to normal tissue oxygenation.

PScap is a measure of unidirectional tracer flux across the capillary endothelium to the myocardial tissue (*11*, *13*,*24*). PScap estimates were unaltered by hypoxia, indicating that tracer movement from the vascular compartment is not influenced by the level of myocyte oxygenation or function. However, in ouabain experiments, a significant decrease in the PScap estimate for thallium implies that capillary surface area available for exchange is reduced or that thallium extraction (Emax) at the capillary level is impeded. Regarding the former possibility, ouabain might reduce exchanging capillary area by increasing coronary resistance (*18*). However, as thallium PScap decreased with ouabain, SESTAMIBI PScap tended to increase (statistically insignificant), which would not support the premise that ouabain induced an overall decrease in exchangeable surface area. Therefore, Na^+/K^+ ATPase inhibition is the most likely cause for the observed decrease in thallium PScap. It is generally accepted that myocardial thallium uptake is mediated in part by the Na^+/K^+ ATPase system (*23*, *25*), but this is not the only mechanism (*26*). The small decrease in thallium PScap may relate to the incomplete inhibition of the ATPase transport mechanism or to the relative insignificance of ATPase transport in thallium exchange compared to other transport mechanisms.

Retention. As an estimate of tracer retention, the Enet function (*27*) measures the net result of tracer influx and backflux between capillary (vascular) and tissue. Enet estimates for SESTAMIBI and thallium are similar despite a lower influx (i.e., PScap) for SESTAMIBI because SESTAMIBI has a lower backflux than thallium during the tail portion of the h(t) curves (Fig. 1). Enet values for SESTAMIBI increased with hypoxia and ouabain, probably from an enlarged extravascular volume of distribution rather than increased uptake since Emax and PScap were not significantly changed for SESTAMIBI by either experimental treatment. For thallium, Enet was unchanged by hypoxia, but a relatively large and progressive decline was noted with ouabain. This decline for thallium probably results from depressed capillary influx (PScap reduced with ouabain, not hypoxia) and from accelerated cellular back diffusion (decreased cellular volume of distribution). More rigorous modeling efforts (*9*) would be helpful in further substantiating these present results.

Clinical Implications

It is important to note that indicator-dilution results and model estimates are not inherently comparable to in vivo clinical studies where recirculation and redistribution effects of tracer play a prominent role. However, these in-vivo experiments permit independent manipulation of factors that would be expected to affect myocardial transport of SESTAMIBI and thallium.

We have observed that transcapillary exchange of thallium is greater than that of SESTAMIBI, but Enet values at control determinations show less disparity. This suggests that the relative high first-pass extraction of thallium compared to SESTAMIBI is somewhat offset by a shorter tissue residence time, resulting in net retention for thallium only slightly greater than for SESTAMIBI. Although hypoxia and ouabain did not induce much change in Emax or PScap for SESTAMIBI or thallium, significant differences were noted in Enet calculations. Therefore, alterations in myocardial cellular function from tissue hypoxia and ATPase inhibition, independent of coronary flow, can affect myocardial transport of these tracers. Specifically, these observations imply that Enet for SESTAMIBI would tend to increase despite a constant coronary perfusion during acute tissue hypoxia and membrane ATPase inhibition. In contrast, hypoxia and ouabain appears to have the opposite effect on net myocardial retention of thallium. Although myocardial transport of SESTAMIBI and thallium are dominated by flow, interpretation of clinical scintigraphic studies should also consider these contributing effects of cellular dysfunction and membrane inhibition.

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