By mimicking hemostatic structural domains of collagen, *Streptococcus sanguis* (aggregation-positive phenotype; Agg \(^+\)) induces platelets to aggregate in vitro. To test the hypothesis that aggregation occurs in vivo, *S. sanguis* (Agg \(^+\) or Agg \(^-\) suspension) was infused intravenously into rabbits. The extent of hemodynamic and cardiopulmonary changes and the fate of circulating platelets were Agg \(^+\) strain dose dependent. Within 45 to 50 s of the start of infusion, \(4 \times 10^4\) CFU of the Agg \(^+\) strain caused increased blood pressure. Thirty seconds after infusion, other changes occurred. Intermittent electrocardiographic abnormalities (13 of 15 rabbits), ST-segment depression (10 of 15 rabbits), and preventricular contractions (7 of 15 rabbits) manifested at 3 to 7 min, with frequencies dose dependent. Respiratory rate and cardiac contractility increased during this phase. Blood catecholamine concentration, thrombocytopenia, accumulation of \(^{111}\text{In}\)-labeled platelets in the lungs, and ventricular axis deviation also showed dose dependency. Rabbits were unaffected by inoculation of an Agg \(^-\) strain. Therefore, Agg \(^+\) *S. sanguis* induced platelet aggregation in vitro. Platelet clots caused hemodynamic changes, acute pulmonary hypertension, and cardiac abnormalities, including ischemia.

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**MATERIALS AND METHODS**

**Experimental design.** To test our hypothesis, apparently healthy New Zealand White rabbits were studied before and after \(t = 0\), when viable streptococci (expressed in CFU) were infused for 1 min (Fig. 1). In each rabbit, a baseline set of hemodynamic and cardiovascular variables was obtained (\(t = 10\) to 0 min), including heart rate, blood pressure, standard three leads of the ECG, respiratory rate, platelet count, and blood catecholamine level. The blood pressure, heart rate, and ECG were then monitored continuously from \(t = 0\) to 7 and at 10, 20, and 30 min. Intermittently, blood was sampled (3 ml each sample) for platelet counts and catecholamine analysis at baseline, \(t = 7\) to 8 (catecholamines only), and \(t = 30\) min. At \(t = 10\) min, \(^{111}\text{In}\)-labeled platelets were infused into the venous circulation of some rabbits. At \(t = 30\) min, the rabbits were euthanized.

**Animal protocol.** All protocols, including euthanization of rabbits, were consistent with the Guiding Principles in Care and Use of Animals of the American Physiological Society and approved by the University of Minnesota Animal Care and Use Committee. Before entering the experimental protocol, rabbits were conditioned by daily gentle handling for 2 to 3 weeks.

Rabbits (diet, Purina Rabbit Chow; age, 5 to 6 months; weight, 3.2 to 4.2 kg; gender, males and females) were anesthetized with intramuscular (i.m.) xylazine hydrochloride (Rompun, 5 to 10 mg/kg of body weight and ketamine, 30 to 40 mg/kg). Supplements of ketamine or nembutal were given to maintain anesthesia, and xylazine was injected intradurally to prevent discomfort during surgical procedures. The femoral vein was cannulated for the infusion of strepto-
cocc. $^{111}$Indium-labeled donor platelets, and the euthanizing agent. Arterial blood pressure was recorded through the carotid artery cannula. Viable S. sanguis cells suspended in sterile, pyrogen-free saline, or pyrogen-free saline alone were infused. Rabbits were euthanized by lethal intravenous injection of nembutal, and the lungs were removed.

**Bacterial strains.** Two representative strains of S. sanguis from our culture collection were selected for study and were described in earlier reports (25, 26). Strain 133-79 was originally isolated from blood culture of a confirmed case of streptococcal endocarditis and was obtained from R. Facklam, Centers for Disease Control Prevention, Atlanta, Ga. This was a biotype I strain according to the phenotyping scheme of R. R. Facklam as described previously (24, 25). Strain 133-79 was originally isolated from blood culture of a confirmed case of streptococcal endocarditis. S. sanguis cells expressed as CFU.

**Calculations, data analysis, and statistics.** To estimate heart work, the average carotid blood pressure multiplied by the heart rate was calculated as described earlier (26). The heart rate-blood pressure product is proportional to the pressure-volume work of the left ventricle or an estimate of the hemodynamic status of the rabbit.

Differences between doses, and Agg$_1$ and Agg$_2$ phenotypes and sham saline groups were ascertained. Percentage change (magnitude) and frequency of change were calculated to facilitate evaluation of dose dependency. The frequency of occurrence was evaluated by linear regression analysis and Fisher exact test (two-tailed), while percentage change (magnitude) was evaluated only by linear regression analysis. Differences in magnitude between baseline and post-bacteremia values were evaluated by the Student t test.

**RESULTS**

Platelet aggregation in vitro. In response to strain 133-79, the mean lag time to onset of rabbit platelet aggregation in vitro was 2.0 min (range, 1.8 to 2.5 min; n = 6 rabbits). Strain L50 failed to induce aggregation of platelets from any rabbit tested.

**Hemodynamic consequences.** Infusion of doses ranging from $4 \times 10^8$ to $40 \times 10^8$ CFU of the Agg$^+$ strain altered blood pressure and heart rate primarily during the first 7 min, which changed the index of cardiac work (Fig. 2A to C). Initial preliminary studies in rabbits suggested that hemodynamic changes would occur as a function of dose (30, 31). Compared to the Agg$^+$ strain, infusion of $40 \times 10^8$ CFU of the Agg$^-$ strain (or physiological saline vehicle) caused virtually no change in any measured parameter and the blood pressure and heart rate remained at baseline values (Fig. 2A and B). The comparatively low Agg$^-$ dose of $0.1 \times 10^8$ CFU was infused into the four rabbits. Hemodynamics did not change from baseline after infusion. In contrast, three rabbits infused with $100 \times 10^8$ CFU of the Agg$^+$ strain became hypotensive within 40 s and the blood pressure approached zero within 7 min. During the first 7 min after infusion of 4 or $9 \times 10^8$ CFU of the Agg$^+$ strain, the blood pressure response was hypertensive (Fig. 2A).
The time of maximal increase in blood pressure was inversely related to dose (r = 0.78; slope different from 0, P < 0.001 by linear regression analysis). Similarly the average maximal percentage increase in blood pressure decreased with increasing linear regression analysis). Similarly the average maximal per-

axis at in 7 of 15. With this dose, changes in the ventricular electrical ST-segment depression observed in 10 of 15 rabbits and PVCs related to dose (r = 0.52; slope different from 0, P = 0.004). After infusion of 40 × 10⁸ CFU (n = 15 rabbits), the blood pressure response was predominantly diphasic, first hyper- and then suddenly hypotensive. During the hypotensive phase, the heart rate was markedly elevated (Fig. 2B).

**Cardiopulmonary consequences.** Within 3 min of initiation of infusion (t = 3 min), rabbits showed electrocardiographic abnormalities that changed over time, often reverting to normal and then abnormal in a single beat. For example, one rabbit showed abnormal electrocardiographic ST-segment depression and alternating premature ventricular contractions (PVCs) in Lead I through t = 10 min (Fig. 3). At t = 20 and 30 min, the heart rate remained elevated and ST-segment depression persisted. In comparison to baseline, the peak systolic pressure is delayed relative to the QRS complex (excitation of the ventricles) and the dichrotic notch in the pressure recording disappears. When seen during the first 7 min postinfusion, ST-segment depression usually continued through 30 min (data not shown). All of rabbits given 40 × 10⁸ CFU of the Agg⁻ strain showed ST-segment depression (Table 1). The most frequent abnormalities were ST-segment depression observed in 10 of 15 rabbits and PVCs in 7 of 15. With this dose, changes in the ventricular electrical axis at t = 30 min were seen in 11 of 15 rabbits (six showed right axis deviation and five left axis deviation). During the 30-min postbacteremia period, rabbits often developed more than one type of abnormal ECG pattern.

In 11 of the 15 rabbits given 40 × 10⁸ CFU of the Agg⁻ strain, the arterial dP/dt increased significantly during t = 3 to 7 min. In contrast, only one of five rabbits showed an increase in cardiac contractility after infusion of 9 × 10⁸ CFU. Since first rabbits studied showed an increase in dP/dt, blood was sampled for catecholamine concentration [CAT] in subsequent rabbits. When both were determined in the same rabbits, the frequency of elevated dP/dt was directly related to [CAT] in blood pressure. Changes ± 4 to 5% were significantly different from zero. The Agg⁻ strain, even at 40 × 10⁸ CFU, did not alter the heart rate during the period of bacteremia. (C) Heart rate. Average percentage change was plotted at the same minute intervals as blood pressure. Changes were shown to occur as a function of infused dose of Agg⁻ S. sanguis. As noted in Fig. 4, cardiopulmonary variables were not influenced by the infusion of the Agg⁻ strain.

**Platelet fate.** If they formed in vivo, then platelet clots should be observed in the lungs (Fig. 5A) and the fate of circulating platelets should be reflected in thrombocytopenia (Fig. 5B). Both of these measures of platelet cloting in vivo were shown to occur as a function of infused dose of Agg⁻ S. sanguis. Platelet clots in the lungs occurred in response to all doses when analyzed at t = 30 min, but appeared to maximize upon infusion of 9 × 10⁸ CFU (Fig. 5A). The FU of ¹¹¹Indium-labeled platelets/g was not significantly different at doses of
9 \times 10^8$ and $40 \times 10^8$ CFU. After infusion of $40 \times 10^8$ CFU of the Agg$^+$ strain, the FU/gram was 3 standard deviations lower than after infusion of $0.1 \times 10^8$ CFU of the Agg$^+$ strain. Platelets cleared from the circulation to the spleen, but the FU/gram of spleen decreased as a function of dose of Agg$^+$ S. sanguis ($r = 0.82$; slope different than 0, $P = 0.003$ by linear regression analysis) (data not shown). The platelet count at $t = 7$ to 8 minutes was generally unaffected by infusion of up to $4 \times 10^8$ CFU of the Agg$^+$ strain (thrombocytopenia in one of seven rabbits) (Fig. 5B). The frequency of thrombocytopenia was 80% after infusion of $9 \times 10^8$ CFU and 100% after $40 \times 10^8$ CFU (data not shown). The percentage decrease in platelet
Police aggregation. The blood pressure and heart rate change than would be predicted by the two minute lag time for in vitro spleen, but the 111Indium-labeled platelets used as tracers do spleen. Platelets normally clear from the circulation to the lungs (Fig. 5), but not in the pulmonary circulation as shown by the association between accumulation of 111Indium-labeled platelets in the lungs with thrombocytopenia (Fig. 5A and B).

In our model, the pulmonary changes and accumulation of 111Indium-labeled platelets in the lungs may underestimate the extent of platelet clots formed or trapped in the pulmonary circulation. Ketamine used in our protocol has been shown to cause ex vivo pulmonary vasodilation in rabbits (39), which would antagonize the accumulation of platelet clots. Hence, the potential for S. sanguis to induce in vivo platelet clotting may be greater than suggested by our data. An important consequence of S. sanguis-induced platelet clotting is ST-segment depression, which indicates heart ischemia (9). Evidence of ST-segment depression first appeared during the hypotensive phase, occurred as early as three minutes after infusion, and generally persisted until term (Fig. 3). All rabbits with 40 × 10^8 CFU showed increased respiratory rate, diphasic blood pressure and thrombocytopenia, but only 13 of 15 rabbits showed abnormal ECGs and only 2 of 3 showed ST-segment depression. The frequency of abnormal electrocardiographic responses may reflect inter-rabbit variation in fibrinogen levels, plasminogen activator activity, platelet reactivity, displacement or disaggregation of platelet clots, or the anatomy and function of the coronary circulation, which might provide restoration of blood flow by reflexive vasodilation. Coronary vasospasm accompanied in vivo platelet clotting in response to intravenous collagen (40). It is unclear if coronary artery vasospasm was reflected in the response to the Agg^+ strain, but a spectrum of vasoactive mediators may be released in response to S. sanguis-induced platelet clotting. Based on the hemodynamic and cardiopulmonary changes, platelet clotting occurred upon infusion of only the Agg^+ strain and not the Agg^− strain of S. sanguis.

During the 30 min of our protocol, platelet clots appear to persist and may become thrombotic. Thrombin, however, requires the generation of thrombin and fibrin. In humans, platelet clots can occur in the absence of initiation of coagulation and the production of fibrin (49). In our model, initiation of coagulation through tissue injury and the cytokine-mediated expression of tissue-factor is unlikely to occur in only 30 min (18, 41). Based on in vitro data, the platelet clots would be expected to contain activated platelets in proximity to the endothelium. Thromboxane A2 released from activated platelets, for example, can “activate” endothelium (48, 57). Coagulation can be initiated on the surface of activated endothelium and platelets, generating thrombin and fibrin (22). The contact factor (intrinsic) system of coagulation can be assembled and activated within minutes on endothelial cells (or platelets).

<table>
<thead>
<tr>
<th>Dose (10^8 CFU)</th>
<th>Total no. of rabbits</th>
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No abnormalities observed after infusion of 40 × 10^8 Agg strain.

Counts was significantly related to dose of Agg^+ S. sanguis (r = 0.83; slope different than 0, P < 0.001 by linear regression analysis). Since Agg^+ strain doses of ≤4 × 10^8 CFU did not cause detectable thrombocytopenia, platelet counts were not completed for rabbits given the Agg^− strain.

**DISCUSSION**

The Agg^+ strain of S. sanguis induces platelet aggregation or clotting in vivo as predicted by the in vitro data. Aggregation in vitro is all-or-none with a dose-dependent delay (23). In vitro, rabbit platelets aggregate in response to the Agg^+ strain in about two minutes. The experiments in vivo had been designed to record hemodynamic and cardiopulmonary responses upon a 1-min infusion of S. sanguis. Direct evidence for platelet aggregation or clotting in vivo include thrombocytopenia and, when compared to the Agg^− strain, accumulation of 111Indium-labeled platelets in the lungs (Fig. 5), but not in the spleen. Platelets normally clear from the circulation to the spleen, but the 111Indium-labeled platelets used as tracers do not. The frequency and extent of manifestations of platelet clotting in vivo increase directly with the dose of inoculated Agg^+ S. sanguis.

Changes in heart rate and blood pressure occur more rapidly than would be predicted by the two minute lag time for in vitro platelet aggregation. The blood pressure and heart rate change 10 to 15 s before completing the 1-min infusion of doses of Agg^+ S. sanguis ≥9 × 10^7 CFU and reach maxima shortly thereafter (Fig. 2). In vivo clots may incorporate red blood cells to increase the rate of accumulating volume and mass when compared to aggregation of only platelet-rich plasma. An early dose-dependent increase in circulating catecholamines would also be expected to potentiate clotting in response to S. sanguis. In vitro, physiological concentrations of epinephrine potentiates human platelet aggregation in response to S. sanguis (27, 37a). The rapid increase in circulating catecholamines may originate from post-sympathetic discharge (19) or endogenous platelet stores (27, 56). Upon release from platelets, thromboxane A2 and serotonin will also potentiate aggregation. Therefore, the changing hemodynamics suggest that platelet clots form earlier and are probably larger in vivo than would have been predicted by in vitro experiments.

Regulated by a negative feedback system, cardiac output is equal to the stroke volume times the heart rate and is dependent upon the blood pressure gradient divided by the total peripheral resistance of the vascular bed. A clot-inducing material like S. sanguis in the vascular bed alters the resistance to flow. In response to Agg^+ S. sanguis, platelet clotting caused increased pulmonary vascular resistance. The reduced venous return promoted the hypotensive phase (Fig. 2A). Ventricular contractility (dP/dt) and heart rate (Fig. 2B) increased to regulate stroke volume and restore cardiac output.

Consistent with the accumulation of platelet clots in the lungs, tachypnea developed rapidly, maximizing within 90 seconds of infusion of 100 × 10^8 CFU of the Agg^+ strain. In response to 40 × 10^8 CFU, tachypnea maximized at about 3.2 min. Platelet clot-associated occlusion persisted in some rabbits, causing pulmonary hypertension. Pulmonary hypertension resulted in right axis deviation of the heart as observed in 6 of 15 rabbits. Even the dose of 9 × 10^8 CFUs of the Agg^+ strain caused tachypnea frequently, but with low severity (Fig. 4C). The magnitude of tachypnea in experimental animals is dependent upon the number of injected glass microspheres and independent of the anatomic region of the lungs to which the beads embolized (32, 34). The responses to experimental embolism appear to be determined primarily by the magnitude of the pulmonary obstruction (45). Hence, tachypnea is best explained by persistent dose-dependent platelet clots in the pulmonary circulation as shown by the association between accumulation of 111Indium-labeled platelets in the lungs with thrombocytopenia (Fig. 5A and B).

In our model, the pulmonary changes and accumulation of 111Indium-labeled platelets in the lungs may underestimate the extent of platelet clots formed or trapped in the pulmonary circulation. Ketamine used in our protocol has been shown to cause ex vivo pulmonary vasodilation in rabbits (39), which would antagonize the accumulation of platelet clots. Hence, the potential for S. sanguis to induce in vivo platelet clotting may be greater than suggested by our data.

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**TABLE 1. Frequency of ECG abnormalities 3 to 7 min after infusion with S. sanguis (Agg^+)**

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No abnormalities observed after infusion of 40 × 10^8 Agg strain.
FIG. 4. Cardiopulmonary consequences of S. sanguis bacteremia. For selected variables, the Agg\(^+\) dose-dependent changes in frequency or magnitude are presented. Two rabbits infused with 0.1 \(\times\) 10\(^8\) CFU of the Agg\(^+\) strain and five with 40 \(\times\) 10\(^8\) CFU of the Agg\(^-\) strain are also included for comparison. Note that the Agg\(^-\) strain had no effect upon any of the cardiopulmonary variables studied. The regression line for each variable shown was significantly different from zero (linear regression analysis). (A) ECG abnormalities at \(t = 3\) to 7 min. During this period after infusion, the ECG was monitored and changes were evaluated for the numbers of rabbits shown. (B) Increases in cardiac contractility (\(t = 3\) to 7 min) and catacholamine concentration (\(t = 7\) to 8 min). Cardiac contractility was computed as dP/dt as described in Materials and Methods. In the same rabbits, catacholamine concentrations were determined by radioenzymatic assay as described in Materials and Methods. (C) Frequency and percent increase in tachypnea at \(t = 3\) to 7 min. Note the high frequency but comparatively low magnitude with an Agg\(^+\) dose of 9 \(\times\) 10\(^8\) CFU. Catecholamines did not vary from baseline in rabbits given Agg\(^+\) doses of 0.1 and 4 \(\times\) 10\(^8\) CFU. Since the cardiopulmonary responses were similar to rabbits given lower doses of the Agg\(^+\) strain, rabbits given 40 \(\times\) 10\(^8\) CFU of the Agg\(^+\) strain were not sampled for catecholamines.
Therefore, the platelet clots may become more thrombus-like over time.

Activation of coagulation would also rapidly generate vasoactive bradykinin and plasminogen activators (47). These products of coagulation may act synergistically with thromboxane A2 and serotonin from activated platelets, and the elevated circulating catecholamines seen after infusion of Agg⁺ S. sanguis, to promote an arteriolar pressor response. Clearly there are several available mechanisms to cause rapid vasoconstriction. In contrast, the norepinephrine pressor response was probably not inhibited by nitric oxide during the hypotensive phase of the diphasic blood pressure response caused by 40 × 10⁸ CFU of Agg⁻ S. sanguis. Nitric oxide production requires several hours for cytokine-mediated gene expression in response to related streptococci or gram-negative lipopolysaccharides (42). S. sanguis caused changes far too rapidly to be explained based on events requiring the translation of genes and synthesis of new proteins. The rapid expression of a set of vasoconstrictors and platelet clotting appear to be sufficient to promote vascular occlusion and contribute to persistent ST-segment depression and heart ischemia in our model. Hence, S. sanguis-induced platelet aggregation in vivo may trigger several complimentary mechanisms to promote thrombosis rapidly in the apparent absence of endothelial or atherosclerotic disease. Thrombocytopenia in response to S. sanguis may suggest the occurrence of disseminated intravascular coagulation (DIC). DIC can occur with gram-negative or gram-positive sepsis (6, 41) and is marked by thrombocytopenia and the deposition of fibrin in the microvasculature. The gram-positive Staphylococcus aureus induces DIC through activation of the coagulation cascade in vivo (36) and correlates with the ability of the microbe to induce platelet aggregation ex vivo (35). In our experiments, fibrin deposition was unlikely to have occurred coincidentally with the sudden hemodynamic and cardiopulmonary changes, or the onset of platelet clotting. Hence, platelet clotting in response to S. sanguis appears to occur in the absence of DIC.

Agg⁺ S. sanguis bacteremias also cause the formation of thrombotic platelet vegetations in the rabbit model of endocarditis (26, 46). The Agg⁺ strain induced the formation of significantly larger vegetations than the Agg⁻ strain. One day after infusion of Agg⁺ S. sanguis, the vegetation was a dense mass of aggregated platelets and fibrin, with few isolated and trapped bacterial cells comprising less than 1/100th of the
cross-sectional area (29). The development of the vegetation could be induced by infusion of specific anti-fibrin antibody (58) or reversed by administration of tissue plasminogen activator (46). Comprised of fibrin and aggregated platelets, the vegetation formed in response to the Agg⁺ strain of S. sanguis was a thrombus. Since aggregation of human and rabbit platelets also occurs in vitro (24, 25, 50) and in vivo, as shown in this study, there are now three lines of evidence that Agg⁺ S. sanguis can be thrombogenic. That S. sanguis experimental bacteria can induce signs of thrombosis and heart ischemia is also of interest because of the possible epidemiological relationship between dental infections and myocardial infarction (5, 8, 44). Individuals in several different populations who have suffered recent myocardial infarction show a greater prevalence of periodontitis, pulp abscesses, and other oral infections than control subjects. Similar findings have also been reported for stroke as an outcome variable (21). The underlying biological basis for these epidemiological findings is unclear. S. sanguis comprises about 30% of the population of bacteria in the complex microbial community of the dental plaque biofilm. Fragments of this biofilm containing S. sanguis and other potentially thrombogenic microorganisms such as Porphyromonas gingivalis (28) are detected as bacteremias often through life (11), although the character and amount of the inoculum is unknown. Since the frequency and magnitude of these bacteremias may increase with the occurrence of chronic infections such as periodontitis, it is tempting to speculate that S. sanguis bacteremias may cause similar hemodynamic and cardiopulmonary changes in humans as shown in rabbits. While the data showed that comparatively low doses of pure cultures of Porphyromonas gingivalis and other potentially thrombogenic microorganisms such as S. sanguis caused in vivo responses, environmental regulation in the biofilm may result in expression of bacteria that are more or less thrombogenic. Platelet clotting in vivo suggests a new and novel paradigm of cardiac dysfunction caused by a nonpathogenic commensal bacteria from the oral cavity.

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